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SYMPOSIUM ON THE CEREBELLUM.

(1) THE CHIEF INTRACEREBELLAR AND PRECEREBELLAR NUCLEI, WITH A DEMONSTRATION OF MODELS AND CHARTS.

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(*New York.*)

The genesis of the chief nuclei connected with the cerebellum in vertebrates, and more particularly in mammals, reveals an evolutionary process which appears to be dependent upon the transition from quadrupedal to quadrumanous specialization, with the final assumption of bipedal and bimanal adaptation.

Some of the cerebellar and precerebellar nuclei illustrate this process more than others. This is true of the nuclei involved in neokinetic development. The nuclei involved in paleokinetic development give less evidence of the evolutionary process.

The following are the groups of nuclei as disclosed by means of reconstruction :—

I. Precerebellar Nuclei.

Group 1. Vestibular complex—(*a*) nucleus of Deiters; (*b*) nucleus of Schwalbe; (*c*) nucleus of Bechterew.

As a complex these nuclei present a striking constancy in proportions, coefficients and configuration among the mammals. They are connected with the vermis cerebelli and associated with the archikinetic activities involved in the function of balance.

Group 2. Inferior olivary complex—(*a*) mesial nucleus and (*b*) dorsal nucleus (paleokinetic); (*c*) chief nucleus (neokinetic).

As a complex these nuclei present a striking variability in their

inter-relations, coefficients and configuration among the mammals. The old olivary group (paleo-olive) is connected with the vermis cerebelli and essential to the co-ordination of paleokinetic activities of such primitive associated movements as those of swimming, crawling, flying, walking, &c. This group has progressively decreased in the higher development of the primates. The new olivary group (neo-olive) is connected with the lateral cerebellar lobes, and is essential to the co-ordination of neokinetic activities, such as the most highly skilled learned movements of the hands and feet. The new olive has progressively increased in size and prominence through all of the intermediate stages of quadrupedal development in the primates up to complete neokinetic attainment.

II. Intracerebellar Nuclei.

Group 1. Mesial complex—(*a*) nucleus fastigii; (*b*) nucleus globosus.

As a complex these nuclei present marked constancy in the mammals. Their coefficients, configuration and dimensions show very little change from order to order. They are related to paleokinetic functions and also to the archikinetic function of balance.

Group 2. Lateral group—(*a*) nucleus dentatus; (*b*) nucleus emboliformis.

This group is much more variable throughout the mammalian orders in coefficients, configuration and dimensions. The dentate nucleus especially is extremely sensitive in this respect, and shows its greatest development in the primates, reaching its most complex form in man.

The lateral group is connected with the neokinetic functions—with learned, skilled movements, particularly associated with the development of the hand.

(2) A COMPARATIVE STUDY OF THE ARBOR VITÆ AND THE FOLIAL PATTERN OF THE MAMMALIAL CEREBELLUM.

BY HENRY ALSOP RILEY, M.D.

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THE varying forms of the arbor vitæ and of the folial pattern were studied in a series of mammalia, and new diagrams were presented of the form and constitution of the folia.

An attempt was made from this study to formulate a conception of cerebellar localization on the basis of the constitution of the cerebellum as compared with the varying morphological and functional equipments of the animals studied.

(This paper will appear in full in the *Archives of Neurology and Psychiatry.*)

(3) THE INFLUENCE OF THE CEREBELLUM UPON THE REFLEX ACTIVITIES OF THE DECEREBRATE ANIMAL.[1]

BY LEWIS J. POLLOCK, M.D.

AND

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(*Chicago, Illinois.*)

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CHAPTER I.—INTRODUCTION.

ANALYSIS of experimental and clinical observations upon the physiology of the cerebellum has resulted in a state of confusion, relating not only to its possible function, but to the definitions of such parts of its functions which may be reflected by symptoms produced by removal or stimulation. In recent years the physiology of the postural functions of the brain-stem has been explained more clearly by those experiments based upon the existence of certain positive reflex functions (tonic and righting reflexes) which disappear when some part of the bulb and mid-brain is destroyed.

Unfortunately, no positive reflex connected with the cerebellum has

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been discovered. Lacking this, it is possible to study certain known reflex activities of the brain-stem of a decerebrate animal in relation to the removal or stimulation of the cerebellum. As was pointed out by Walshe [1], the observations upon the effect of ablation of the cerebellum upon the postural tone of a decerebrate animal seem only to increase the difficulty of attributing to the cerebellum the function of regulation and integration of all the elements concerned in the maintenance and regulation of posture. Sherrington [2] pointed out many years ago that the rigidity of a decerebrate animal is not abolished by ablation of the cerebellum, and his experimental results have been amply corroborated. (Magnus and de Kleijn [3], Beritoff [4].) It does not follow that in an intact central nervous system the cerebellum may not be shown to regulate the postural tone evoked by the labyrinth or other reflexes.

Assuming that the sum total of function of that part of the brain-stem remaining after decerebration was expressed in the resulting rigidity in an antigravity position, former workers were largely concerned with attempts to abolish the rigidity by ablation of the cerebellum, red nucleus, eighth nerves, and other parts of the nervous system which remained intact. If it had been assumed that the antigravity position was but the result of one particular group of numerous reflexes which could be released from the brain-stem, the direction of research would have been modified. Beginning with such an assumption, one might speculate that the standing reflex of decerebrate rigidity is one of the simplest patterns which may be released. If other patterns are present, they are either inhibited or cannot break through the extreme extensor rigidity which is ordinarily present. Investigation should deal largely with attempts to release other patterns by removal of the remaining parts of the nervous system which either inhibit them or, by selective influence upon extensor tone, prevent their appearance. Regulation does not necessarily imply reinforcement, and one may look as logically for increase or dissociation of tonic postural reflexes as for their disappearance. If, as shown by Rademaker [5], the normal distribution of tone in a mid-brain animal depends upon the integrity of the red nucleus and rubro-spinal tracts, the reflexes released from caudal portions of the nervous system can modify that abnormal distribution of tone only as to its pattern and reciprocal innervation.

This study consists of observations upon the modification of the reflex activities and postures of a decerebrate animal produced by destruction of the labyrinths, cerebellum, and parts of the brain-stem.

Chapter II.—Description of a Method of Decerebration by Anæmia.

In 1896 Sherrington described the condition of decerebrate rigidity which follows transection of the brain-stem between the anterior and posterior colliculi. Following this, decerebrate animals have been produced chiefly by ablation of the cerebrum, or by transection of the brain-stem.

These mutilating operations are attended by a high mortality, and are associated with a great degree of shock. The exact level of decerebration cannot be predetermined, and a complete decerebration is not assured until post-mortem examination. Frequently some part of the brain cephalad to the decerebration remains intact. Bleeding is difficult to control and the degree of hæmorrhage is immeasurable. Shock obscures the picture and the time of its disappearance cannot be determined accurately. An animal decerebrated by such methods shows symptoms which result not only because of the removal of function of certain parts of the brain, but also because of compression, which is the result of hæmorrhage and mutilation of an immeasurable area of nervous tissue adjacent to the operative wound.

It has been shown by Hill [6] that occlusion of the blood-supply to the central nervous system for fifteen minutes produces damage from which there can be no recovery. This has been corroborated by many workers, and Stewart, Guthrie, Burns and Pike [7] produced excellent spinal animals by the combined occlusion of the vertebral and carotid arteries. Often they were obliged to ligate the right innominate and the left subclavian arteries as well. It follows that if a method could be devised whereby an anæmia of a certain isolated part of the cerebrum could be produced for a period of time longer than fifteen minutes, that part of the brain would be rendered functionless.

Studies upon comparative anatomy have shown that the cerebral arteries are laid down with remarkable precision, and the distribution is associated closely with the function of the parts supplied. According to Stopford [8], who studied the distribution of the blood-vessels to the pons and medulla by means of injection experiments, the nutrient vessels to the pons and medulla are true end arteries and may be utilized in the investigation of function of certain parts of the medulla and pons. It is possible, then, in the absence of anastomotic vessels, to interrupt the continuity of the blood-stream in the basilar artery by a ligature, and thus separate that part caudad from that cephalad to the ligature. If

the carotid arteries are then tied a complete anæmia of the brain cephalad to the ligature upon the basilar artery is produced (fig. 1).

Method.—In a former communication we have published a description of an operation to produce an anæmic decerebrate animal [9]. The method of decerebration by anæmia consists of two steps: first, the ligation of the basilar artery at any desired level and, second, the ligation of the carotid arteries.

Cats were used throughout as the experimental animals of choice. The method is also suited for monkeys, and excellent preparations were

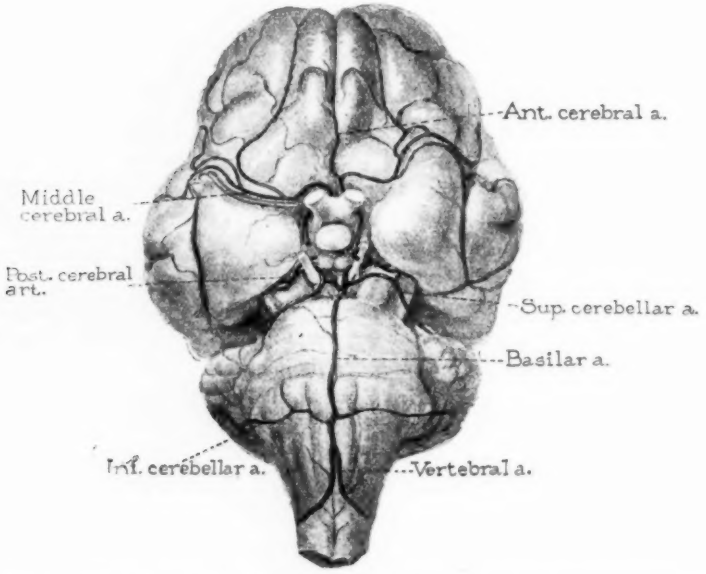

FIG. 1.—Drawing of the basal surface of the cat's brain showing the arrangement of the vessels.

obtained in this animal. After the animals were anæsthetized with ether in the usual manner, they were tied to an operating table with the ventral aspect upwards. A small catheter was introduced into the trachea and connected with an ether bottle, through which a stream of air was directed. The ether bottle was so arranged with valves that any desired stage of anæsthesia could be secured and maintained.

A mouth gag was fixed in place and the jaws widely separated. This also served as a means of securely fixing the animal's head in position. A ligature was passed through the median line of the tongue, and that organ held outside the mouth. A median line incision was made in the soft palate from the posterior edge of the hard palate posteriorly. The mucous membrane and muscles were then separated from the base of the skull, posteriorly, to expose the anterior border of the foramen magnum, and laterally to expose the tympanic bullæ. The two flaps of mucous membrane and muscle thus made were retracted by ligatures. It is very important to obtain a clean field, which is free from tags of mucous membrane and muscle, and to expose the tympanic bullæ. The latter bony prominences serve as valuable points of localization in the later operative steps. Opposite these structures one reaches a level in the pons which corresponds to the exit of the fifth pair of cranial nerves.

A motor-driven dental burr was used to trephine through the base of the skull (ventral surface of the body of the sphenoid, basisphenoid and basioccipital bones), and to expose the dura mater covering the pons and the basilar artery with its branches. This method of trephining was found to be very satisfactory, since it tended to stop any bleeding from the edges of the bone. This procedure was continued until a membrane-like layer of bone remained. This was then carefully removed by the use of a very fine spatula. The basilar artery was now visible, lying beneath the dura mater. A dural hook was used to open the dura mater and allow the escape of cerebro-spinal fluid. The basilar artery could be seen clearly in the mid-line of the pons, and its side branches could be distinguished easily.

After the basilar artery had been exposed at the level desired, a strabismus hook, into the end of which a fine hole had been drilled, was used to place a fine silk ligature about the vessel. With care the artery can be ligated without the slightest trauma to the underlying brain-stem. The common carotid arteries were exposed in the neck by a median-line incision and separated from the vagus nerve and internal jugular vein. They were then tied with silk ligatures.

The level of the section obtained by the production of anæmia may be accurately determined by the peripheral intravenous injection of vital stains. A definite differentiation is produced between the normal and the anæmic parts of the brain which remain colourless. Fig. 2 shows the level commonly obtained by the intravenous injection of methylene blue or indian ink, when the basilar artery was ligated at

the level of the exit of the fifth cranial nerves. It will be seen that the superior half of the cerebellum remains unstained. Therefore, this preparation, in addition to being decerebrate, caused a removal of the function of the superior part of the cerebellum. If the basilar

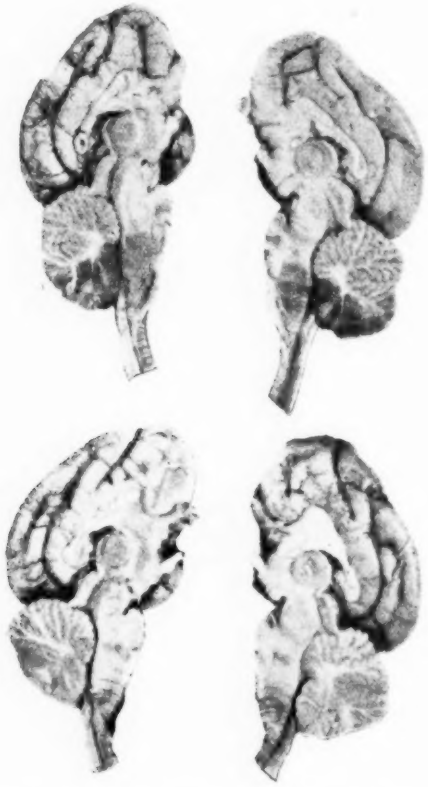

FIG. 2.—Photographs of sagittal sections of cats' brains which had been injected intravenously with Indian ink. The upper sections show the level of the anæmia in an ordinary ligation, the lower sections show the level of the anæmia in a ligation below the inferior cerebral arteries.

artery is tied at the junction of the vertebral vessels the entire cerebellum may be rendered anæmic. Whether half or all of the cerebellum was excluded from the circulation, the decerebrate rigidity seemed in no wise influenced.

Chapter III.—Description of an Animal decerebrated by the Anæmic Method.

Without exception, decerebrate rigidity similar to that described by Sherrington has resulted after ligation of the basilar and carotid arteries. This rigidity varies as to onset and degree, depending upon certain conditions, such as the sequence of arteries tied, time elapsing between their occlusion, position and condition of the animal.

When fully developed the rigidity is marked; the spine is extended, the tail is held in a horizontal position or is curved strongly upward, at times to the degree of lying parallel to the back. Any attempt at depressing the tail is followed by immediate resumption of its original position. The extremities are fully outstretched; the fore-legs are held

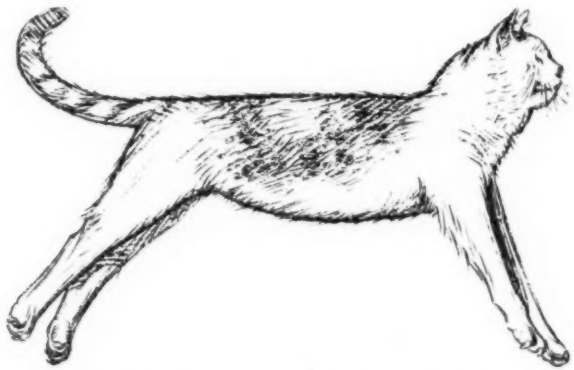

Fig. 3.—A suspended anæmic decerebrate animal. (Drawing after photograph.)

quite stiffly extended at the shoulder and elbow joints and are retracted. The angles between the limbs and the body vary as to the position of the body; if the animal is placed as if sitting on its haunches, the angle is smaller than if the trunk is horizontal. The wrist-joints are seldom involved in the rigidity. The hind-legs are thrust backward and outstretched, but to a lesser degree. All the joints in the hind-legs are involved equally in the rigidity. The head is maintained in a lifted position despite gravity, and there may be some opisthotonos of the head upon the neck. The degree of opisthotonos may be increased by pressure against the outstretched fore-legs or by moving them forward. The jaws are tightly closed. Considerable force is required to produce

flexion of the extended extremities, and when released they immediately assume their former position. Such an animal, if carefully posed, can be made to stand. Numerous reflex reactions may be demonstrated. The body temperature of these animals does not diminish immediately, but usually there is a gradual decrease to the time of death. Some animals have had a rectal temperature of 35·5° C. five hours after decerebration. In fact, one animal had a temperature of 41 C.° six and a half hours after decerebration. The animals are easily overheated, and the use of the heating pad on which the animal lies raises the temperature rapidly. When the pad is removed, the body temperature does not fall, but often rises to a degree of hyperthermia sufficient to produce death (fig. 3).

Chapter IV.—Description of some Reflex Patterns in Decerebrate Animals before and after Removal of the Cerebellum.

(1) *The Pattern and Degree of Extensor Rigidity and Reflex Standing.*

In the decerebrate preparation produced by the ligation of the basilar and carotid arteries the superior part of the cerebellum is functionless. When the inferior cerebellar arteries are electrocoagulated, tied, or severed, the function of the entire cerebellum has been destroyed. If the preparation is made by a ligation of the basilar artery distal to the inferior cerebellar arteries, the cerebellum does not function. In both of these types of preparations the pattern and degree of rigidity were the same, and the preparation could not be differentiated by its appearance from a good Sherrington preparation.

(2) *Lasting Patterns of Rigidity in Flexion produced by Removal of the Labyrinths.*

Maintained flexion of the arm in a decerebrate monkey has been described by Brown [10]. The pattern of rigidity is dependent undoubtedly upon the functional activities of the brain-stem of the particular animal studied. In the decerebrate sloth, which hangs dependent from trees, lasting flexor rigidity in a pattern of reflex hanging following decerebration has been described by Richter and Bartemeier [11]. In monkeys, decerebration by the anæmic method was characterized by a constantly flexed position of the arm. Extensor rigidity could be produced by suitable stimuli, such as pushing upon the passively extended wrist.

Occasionally flexor rigidity has been noted in decerebrate animals by other workers. Bazett and Penfield [12], working upon chronic as well as upon acute decerebrate preparations of the cat, found that an extensor rigidity might alternate with one of flexion. Further, that the more chronic the preparation the more tendency there was for a flexed position to appear. "In the chronic preparations they (i.e., rigid flexed positions) are a comparatively common occurrence. . . ." They stated that "the term decerebrate rigidity is generally taken to mean extensor rigidity. But in completely decerebrated specimens another type of rigidity sometimes appears, tonic contraction of the flexor aspect of the limbs. . . . It would be more accurate, therefore, to speak of extensor and flexor rigidity as two types of decerebrate rigidity." Our experiments upon labyrinthineless decerebrate animals corroborate this statement. Not only do these two types exist, but they can be produced at will in the same animal upon proper stimulation.

The function of the labyrinths has been identified with muscle tone since the early investigations of Flourens, Goltz and Ewald. Whereas these early investigations dealt chiefly with the general influence of unilateral and bilateral extirpations upon tone, co-ordination, and synergy, more recent studies have been concerned with the relation of labyrinthine function to reflex tone. Such studies have been made upon normal and decerebrate animals. We owe much of our knowledge of the rigidity of decerebrate animals to Sherrington's accurate observations and physiological interpretations. The labyrinth was considered by Sherrington [13] to be a receptive organ capable of being stimulated by change of position of the head in relation to the horizon, and by movements of the head. Reflexes which adjust the segment to the horizon line are initiated by the labyrinths. Other structures, such as the extra-ocular muscles, are adjusted by it in a similar reflex manner. He also called attention to the resemblance between the labyrinthine receptors and the proprioceptors of the limbs, in that in both stimulation occurs chiefly through the reaction of the organism itself, and that both originate and maintain tonic reflexes in the skeletal muscles. The observation of Sherrington that movement of the head in relation to the trunk modifies the distribution of extensor tone in the extremities, has been explained fully by the extensive and illuminating researches of Magnus and his co-workers. They have shown that the position of the head determines the distribution of tone in the muscles of the neck, trunk and extremities in intact as well as in decerebrate animals [16]. This influence

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depends upon certain reflexes, of which two chief groups have been described : the standing reflexes and the righting reflexes.

When a decerebrate animal's head is immobilized in relation to the body, and is placed so that the vertex is down and the line of the mouth is at an angle of 45 degrees with the horizontal, the rigidity reaches its maximum. If the vertex be placed up and the line of the mouth is at an angle of 45 degrees below the horizontal, the rigidity is at its minimum. When the labyrinths are destroyed, change of position of

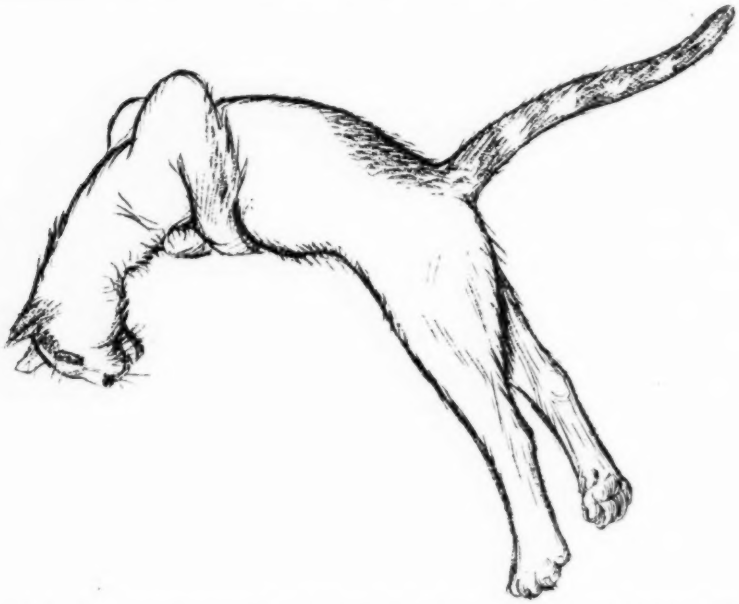

FIG. 4.—A suspended anæmic decerebrate animal following destruction of the labyrinths. (Drawing after photograph.)

the head in relation to space produces no change in the distribution of tone in the decerebrate animal. Such a change, then, is due to the labyrinthine tonic or standing reflexes.

Previously we [15] have described the results of destruction of the labyrinths in animals decerebrated by the anæmic method. When suspended, such an animal assumed a good decerebrate rigidity in fore- and hind-legs. Shortly afterward the head began to drop and the rigidity lessened in the fore-legs. At this time, if the head was passively extended and suddenly released, it dropped into a position of

flexion and the fore-legs were convulsively flexed in all joints and adducted. At the same time, the hind-legs were extended backward more rigidly. If the head was extended passively, again the fore-legs assumed an attitude of extension and the tone in the hind-legs was diminished (fig. 4).

From this it would appear that the labyrinths exert a strong influence upon the extensor reflex of the neck, which tends to produce a fixed position of the head in extension with a consequent marked extensor rigidity in the fore-legs. Not only does this position evoke an extensor rigidity in the fore-legs, but the play of labyrinthine tone upon the extensors of the neck is sufficient alone to reinforce the extensors of the fore-legs when the head is flexed passively in an ordinary decerebrate animal. When the labyrinths are destroyed and the head is suddenly released, marked and sudden flexion occurs as the result of gravity, and the fore-legs are flexed and adducted. The rigidity in flexion is as great as is the rigidity in extension in the ordinary decerebrate animal. The position of the fore-legs in flexion is retained indefinitely until the head is extended passively, or until some phasic reflexes are elicited. Removal of the cerebellum does not affect the pattern of rigidity in flexion in these animals.

(3) *Co-existence of normally distributed Tone; Patterns of Rigidity in Extension and Flexion; Crawling, Climbing and Springing in Animals in which a Segment of the Basilar Artery had been isolated by two Ligatures some Distance apart, and in Animals decerebrated by Ligation of the Basilar Artery at a relatively high level.*

It is obvious that many postural reflexes must exist in a normal animal other than the tonic reflexes. When an animal was decerebrated cephalad to the mid-brain, with or without the thalamus intact, it was found by Magnus [14] that as the animal recovered from shock and ether it gradually assumed a sitting position, and the head, closely followed by the trunk, was brought immediately into a normal position. The distribution of tone was normal. Left to itself, such an animal remained motionless, but could be stimulated to walk, run and jump. If overturned it righted itself, and in whatever position the animal was placed the head at once assumed the upright, normal posture. The ability to assume and maintain the normal position of the body is dependent upon a group of reflexes, the sum total of which is designated as "righting reflexes" (*Stellreflexe*), as opposed

to the tonic reflexes grouped together as "standing reflexes" (*Stehreflexe*). They consist of (1) labyrinthine reflexes acting on the head; (2) postural reflexes arising in the body and acting on the head through asymmetrical stimulation; (3) neck reflexes; (4) postural reflexes acting on the trunk and limb muscles through asymmetrical stimulation. With the exception of the neck reflexes their centres are in the mid-brain.

It was evident from the study of the labyrinthineless preparations that at least patterns of tonic postural reflexes could be elicited from that part of the brain-stem functioning in an ordinary decerebrate animal. We were now concerned with the possibility of releasing other reflexes, and determining what factors inhibited the predominance of labryinthine tone when higher levels of the brain-stem remained intact. In the course of some unpublished work on epilepsy it was necessary to isolate a segment of the basilar artery by ligatures placed some distance apart. During the same work animals were decerebrated by a ligation of the basilar artery much higher than in our ordinary animals. The preparations which resulted from both of these procedures showed very great activity. The experiments were therefore repeated.

Observations.

In one group of animals a double ligation of the basilar artery only was made. In the second group a ligation of the basilar artery was made just posterior to the pituitary fossa and the carotid arteries were then tied. Curiously, the resulting preparations resembled each other very closely. Lying on its back, following the operation, the animal gradually extended the extremities, but the extension of the fore-legs was more marked. After the animal was taken from the operating board and placed upon its side, tone became greater in the uppermost side, and the head became anteflexed. Strong flexion of the fore-legs and paws with unsheathed claws occurred, so that at times the animal grasped its own face and was unable to release it, at which time it cried out. If turned from side to side rapidly it attempted to right itself by rapid movements of the fore-legs; that is, if turned from left to right the left fore-leg abducted and extended. If the animal was turned upon its back with the head spontaneously fixed and was then released, it attempted to roll forward as if to get into a ventral position. If placed upon its abdomen, the fore-legs were in a position similar to the kangaroo position of flexion. Frequently such a preparation attempted progressive movements. If placed in a cage it crawled along the wall and then would spring forward, clasping the wire net of

the cage. It might crawl up the net *until the head became extended. Then rigidity in extension in the fore-legs occurred, and the animal remained immobile until gravity overcame its grasp upon the cage wall and it toppled backward to the floor.* Again, such a preparation would right itself and again would crawl and spring. Springing could be evoked by placing the animal in the position of sitting on its haunches, and by holding it up by the fore-legs and lowering it to its hind-legs. If it was placed upon its abdomen and was pulled backward, it attempted to crawl forward. If it was placed upon its side and the head was rotated passively with the occiput down, a marked rigidity in extension occurred in the fore-legs. This demonstrated an intact labyrinthine tonic reflex. If the head was turned chin to the floor, marked running movements and clawing occurred, and the animal would spring forward, right itself and crawl until it was directly upon its abdomen. There it would rest, with tone apparently normally distributed. Tonic neck reflexes could be elicited. If the animal was suspended, marked running movements occurred, so wild at times that the hind-legs would be caught by the claws of the fore-paws. If, then, the head was passively extended and the fore-legs extended, a typical decerebrate rigidity with reflex standing was produced. Withdrawal, crossed reflexes, clawing, sneezing, pinna and vibrissæ reflexes were present. In both cases we were dealing with an anatomically decerebrated animal, which showed the recognized attitude of decerebrate rigidity in extension in the fore-legs; which at times had normally distributed tone; decerebrate rigidity in flexion in the fore-legs which appeared at times and was sustained; spontaneous crawling, springing, and some righting movements. In the animals decerebrated by a high ligature of the basilar artery and occlusion of the carotid arteries, the superior part of the cerebellum was functionless, and in those in which a double ligature was applied the inferior part of the cerebellum was functionless. It is apparent that decerebrate rigidity in extension or flexion and righting movements may occur whether either the superior or the inferior part of the cerebellum is functionless.

Several decerebello-cerebrate animals also were prepared by a high ligation of the basilar artery and ligature of the inferior cerebellar and carotid arteries. In these animals the labyrinthine tonic reflexes were very pronounced. The rigidity in extension of the fore-legs was very marked when that pattern was released. Otherwise, the animal acted exactly as did an animal with the basilar artery ligated at a high level and with the carotid vessels occluded.

Chapter V.—Co-contraction and Reciprocal Innervation in Synergic Muscular Units are dependent upon Function of a Particular Reflex. Removal of the Cerebellum has no Effect upon the Functional Relation of Antagonistic Muscles.

Tilney and Pike [17] have proposed the conception of a simultaneous contraction in the operation of synergic muscular units, and attribute to the cerebellum the important rôle of maintaining the proper relation in the synergic units of the body. "Its proper function seems to be proportional adjustment in time and extent of the increment of muscular tension."

This work again brings to our attention the controversial subject of the functional relations of antagonistic muscles. In their work, Tilney and Pike were concerned with voluntary action, and experimentally produced movement by electrical stimulation of the cerebral hemispheres, mid-brain and spinal cord. Obviously, the movements which result from such electrical stimulation differ widely from those produced by reflexes induced by peripheral stimulation. It is unnecessary to review the literature upon the functional relation of antagonistic muscles, since Tilney and Pike have presented it adequately and critically. It is interesting, however, to refer to their quotation of the results of Beaunis' experiments: "His analysis seemed, therefore, to show three distinct varieties of intermuscular relation during contraction; first, the antagonists or groups of antagonists contract simultaneously. This is the normal case and, according to Beaunis, by all means the most frequent. Second, a single one of the two muscles may contract while the other remains motionless. This is an exception. Third, one of the muscles contracts and the antagonist lengthens and relaxes."

It is our purpose to show that in so far as tonic labyrinthine and neck reflexes and certain nociceptive reflexes are concerned, all three varieties may be obtained at will in the same synergic unit under certain conditions, and that the removal of the cerebellum does not affect this type of functional relation.

Much of the difference of opinion in regard to reciprocal action of antagonistic muscles is due to difference and faults of technique. Some is due to an attempt to compare one type of movement with an entirely different one; for example, that produced by cortical stimulation with that produced by peripheral stimulation or voluntary movement.

Further discrepancies may be attributed to confusion of the type of stimulus and character of the reflex arc; for example, proprioceptive and tonic reflexes as compared to nociceptive reflexes.

Although, from a study of parts of certain reflexes and movements produced by electrical stimulation of the cerebral cortex and extra-ocular

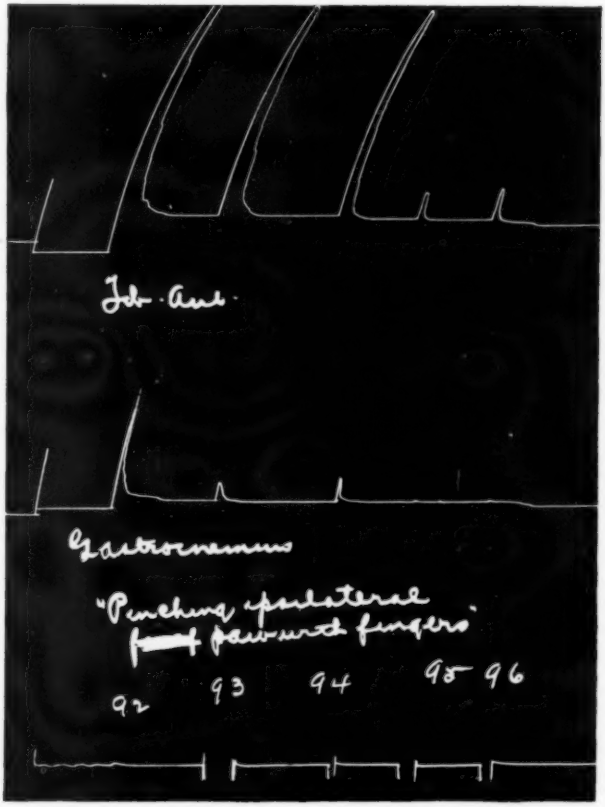

FIG. 5.—Co-contraction resulting from pinching ipsilateral hind-foot with finger in a spinal animal.

muscle movements, Sherrington [18] presented convincing evidence of reciprocal innervation, he recognized that a "change of internal conditions may presumably convert an intra-spinal condition that under the primary conditions is inhibitory, into one that later under supervening

conditions becomes excitatory. The fact that under certain forms of cerebral action true antagonistic muscles can be thrown synchronously into contraction points to the same limitation of the term 'specific' in this condition."

Beritoff [19] has shown conclusively that at the period of intense extensor rigidity in a decerebrate animal, the tonic reflexes chiefly

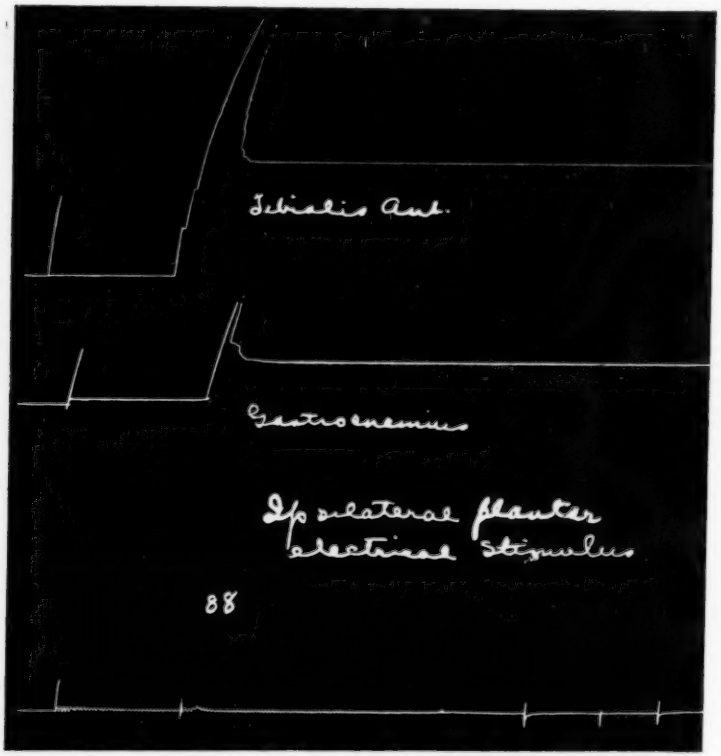

FIG. 6.--Co-contraction resulting from electrical stimulation of ipsilateral planta in a spinal animal.

assume the form of increase or decrease of this "spontaneous" extensor rigidity. The amplitude of tonic contraction of the extensors increases or decreases according to the position of the head. The flexors remain all the while in complete repose; that is, both when the position of the head is optimum for the extensor tonus and when that position is

reversed. At this time ipsilateral sensory nerve stimulation produces a much weaker effect than when extensor rigidity is considerably reduced. When extensor rigidity is weakened with the head in a position favourable for flexor tone (vertex up), contralateral sensory nerve stimulation produces but a feeble contraction of the extensors, but

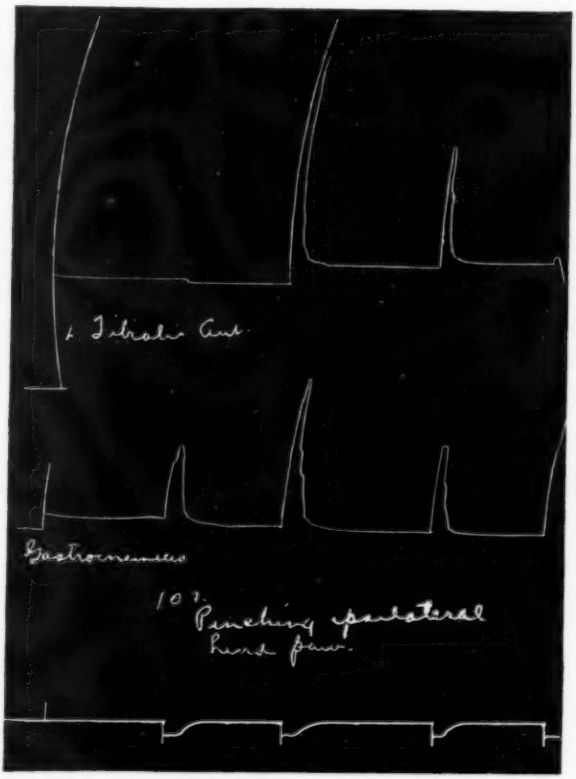

FIG. 7.—Co-contraction resulting from pinching ipsilateral hind-paw in a Sherrington preparation.

when the head is turned vertex down a strong contraction results. This reciprocal relation of antagonists does not relate particularly to the simultaneous contraction or relaxation of antagonistic muscles, but largely to the reciprocral increase or decrease of tone and stimulability in

opposing muscles when the tonic labyrinthine reflexes augment their respective tone.

Beritoff [20] later studied the rôle of labyrinthine and neck reflexes in reflex action evoked by peripheral stimulation in the decerebrate preparation. Here he called attention to the observation of Graham Brown, that in the ipsilateral flexion effect of the decerebrate preparation it often occurs that contraction appears in the extensor as well. Beritoff showed this contraction to be dependent upon the position of the head. The extensor contraction which occurred simultaneously

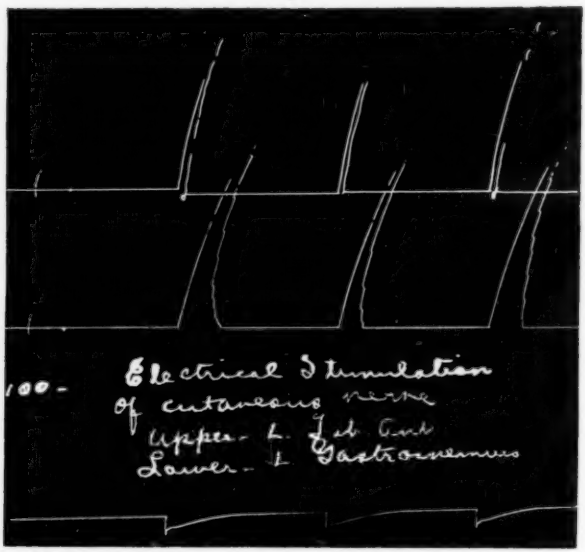

FIG. 8.—Co-contraction elicited by electrical stimulation of ipsilateral sensory cutaneous nerve in a Sherrington animal.

with the flexor one upon ipsilateral stimulation, when the head was twisted face upward, failed to appear when the head was twisted face downward. In the ipsilateral extensor reflex produced by weak stimuli, a slight flexor contraction was noted preceding and at times during the extensor contraction. The amplitude of this contraction depended upon the position of the head. This so-called "decerebrate type" of reflex curve must be regarded as the result of simultaneous excitation of the protective flexion reflex, and of the tonic extensor

reflex from the influence of the neck and labyrinthine extensor centres. In his communication, in 1914, he called attention to non-tonic reflexes preceding the tonic ones when the head was turned from side to side. " In some preparations, a transient contraction of both antagonistic muscles preceded the tonic reflexes, and at the same time the tonic reflexes themselves appeared with distinct reciprocal relations." All this shows that rapid change in the position of the neck produces,

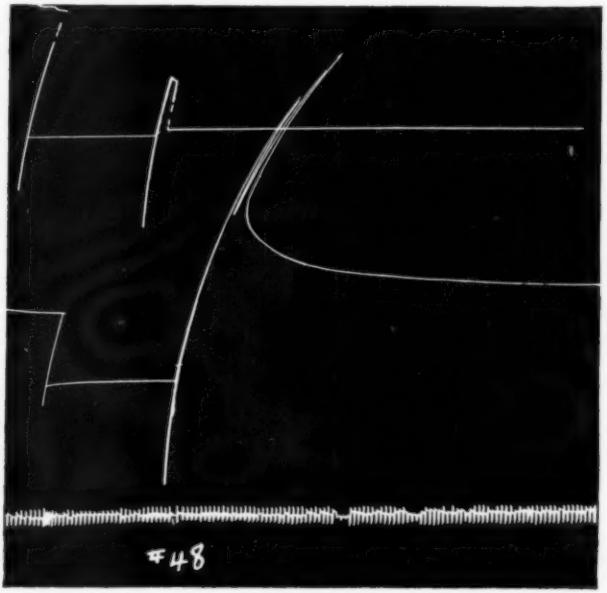

FIG. 9.—Co-contraction elicited by pinching ipsilateral hind-paw in an anæmic decerebrate animal. Upper tracing is from the quadriceps tendon; lower tracing is from the biceps tendon. Abscissæ were drawn upon the kymograph drum.

together with purely tonic reflexes, special reflexes the character of which is not tonic.

Although he does not analyse his tracings for special evidence of co-contraction or reciprocal innervation, an examination of the tracings illustrating his articles shows that co-contraction occurs in the non-tonic reflex preceding the tonic one, in the ipsolateral extensor reflex, in ipsolateral flexor reflexes with and without removal of the cerebellum, and in a contralateral extensor reflex. It is notable that in most

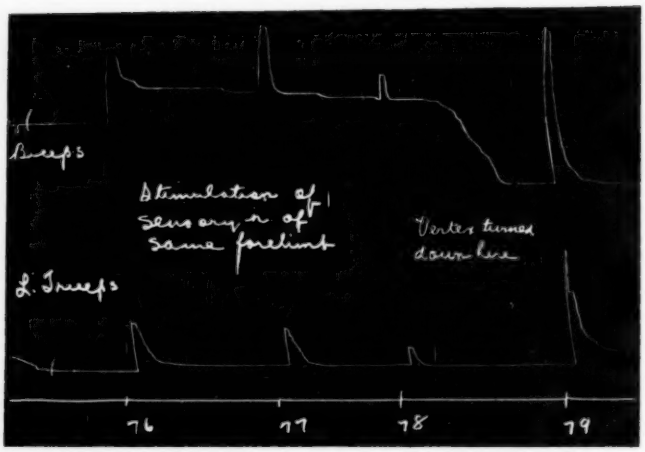

FIG. 10.—Co-contraction elicited by electrical stimulation of an ipsilateral sensory cutaneous nerve in a decerebro-cerebellate animal. Animal lying on its left side. Upper tracing is left biceps tendon; lower tracing is left triceps tracing. When the vertex was turned down, succeeding sensory stimulation produced marked increase in amplitude of contractions in opposing muscles.

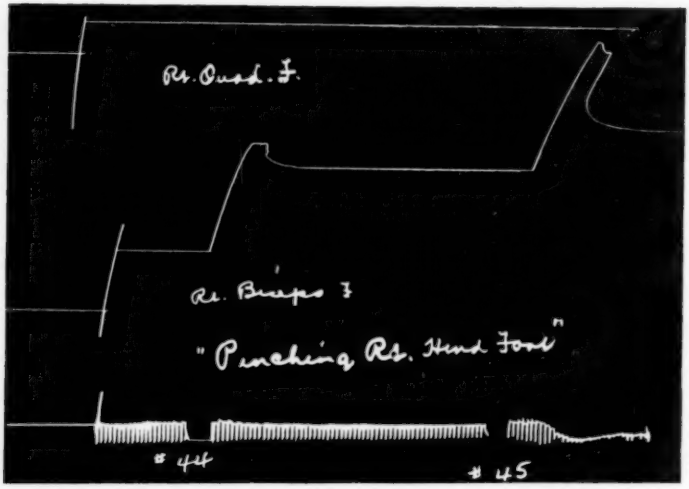

FIG. 11.—Absence of contraction or relaxation in quadriceps tendon accompanying a flexor reflex induced by pinching the right hind-paw in a decerebrate animal when the tone was flexor in character.

instances after the initial co-contraction, when the extensor relaxed, the flexor showed an increment of tone and vice versa. The changes in tone consequent to turning of the head, which were tonic in nature, all showed reciprocal innervation.

Observations.

Our material consisted of spinal animals, animals decerebrated by the anæmic method, and by a saw, before and after removal of the

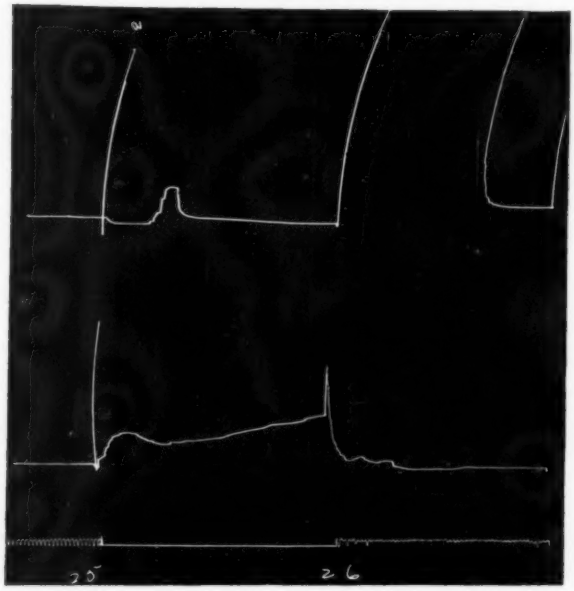

Fig. 12.—Decerebrate animal lying on its left side. Upper curve is biceps tendon; lower tracing is triceps tendon.

In Experiment 25, when the head was turned vertex down a contraction of the triceps resulted. When relaxation ensued an increment of tone was noted in the biceps. In Experiment 26 a co-contraction in antagonistic muscles resulted when the head was turned with the vertex to the right. As the increase of tone continued in the biceps, there was an immediate relaxation in the triceps. The co-contraction resulted from a non-tonic and the reciprocal innervation from a tonic reflex.

cerebellum. In the anæmic decerebrate animals the cerebellum was rendered functionless by cutting, coagulating or tying the inferior cerebellar arteries; the superior cerebellar arteries already being functionless as the result of the carotid and basilar artery ligatures.

The muscle preparations were made with particular care as to careful

separation of muscle planes, conservation of nerves and fixation of all segments about joints by pegs driven through the bones into the animal board. Linen sutures were placed in the severed tendons of antagonistic muscles and fastened directly to a muscle lever to which a counterweight was applied.

Our results may be tabulated under three headings: spinal animals, decerebrate animals, and decerebro-cerebellate animals.

The spinal animals were studied for the purpose of orienting ourselves as to technique and only an ipsilateral sensory stimulus was used. Co-contraction occurred in the tibialis anticus and gastrocnemius

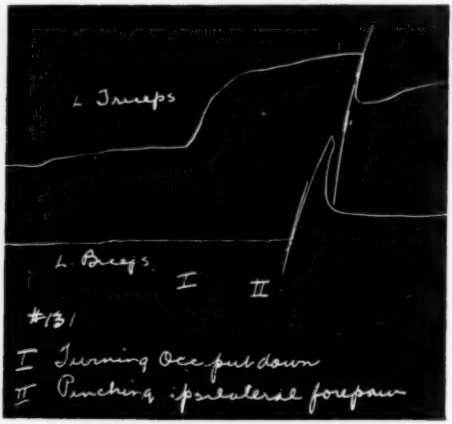

FIG. 13.—Sherrington preparation. Upon turning the vertex down an increment of tone is observed in the triceps. When at "II" the ipsilateral fore-paw is pinched, a contraction in the biceps occurs with a simultaneous relaxation in the triceps. Abscissæ were drawn upon the kymograph drum.

muscles, both upon pinching the hind-paws with the fingers or forceps and upon stimulating the planta or a cutaneous sensory nerve with an induced current (figs. 5 and 6).

Decerebrate animals, whether produced by the anæmic method or by a saw, showed co-contraction upon ipsilateral stimulation of the paw by pinching and upon electrical stimulation of the planta, or of a sensory cutaneous nerve (figs. 7, 8 and 9).

The influence of the labyrinthine tonic reflexes upon the strength of phasic reflexes is illustrated in fig. 10. In this experiment, when the head was turned vertex down and extensor tone increased, the amplitude

of the contraction of the muscles was heightened. When the distribution of tone was flexor in character, simultaneous contraction did not occur in the opposing extensor (fig. 11).

When the head of a decerebrate animal lying on its left side was turned vertex down a contraction of the extensor resulted, and when relaxation in the extensor ensued there was an increment of tone in the flexor. When the head was turned vertex to the right a simul-

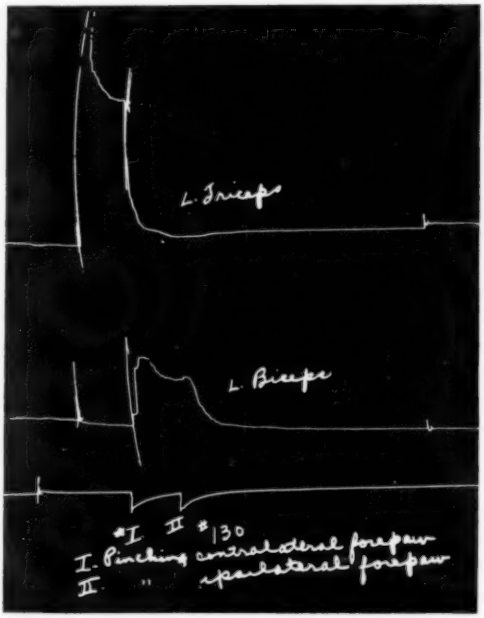

FIG. 14.—Sherrington preparation. "I" pinching contralateral fore-paw produces a contraction in the triceps and no movement in the biceps. A flexor reflex is induced by ipsilateral pinching at "II" and produces a simultaneous relaxation in the triceps. Abscissæ were drawn upon the drum.

taneous contraction occurred in antagonistic muscles as the result of a non-tonic reflex; then, as the biceps continued to contract, the triceps relaxed (fig. 12). At times such an initial contraction slightly preceded the contraction of the biceps.

It was observed that when a tonic reflex was evoked by turning the head, and subsequently a reflex was elicited which would produce a contraction of the opposing muscle, reciprocal innervation was the rule.

Fig. 13 shows an increase in tone in the triceps when the head was turned vertex down. If the ipsilateral fore-paw was then pinched, a contraction occurred in the biceps, and a simultaneous relaxation in the triceps was seen. It will be noted in the tracing that the levers are not directly superimposed, but the abscissæ were made upon the drum.

When an increase of tone was induced by a contralateral reflex, such as pinching the paw, and tone was then sustained, a subsequent flexor reflex (ipsilateral pinching) produced reciprocal innervation with

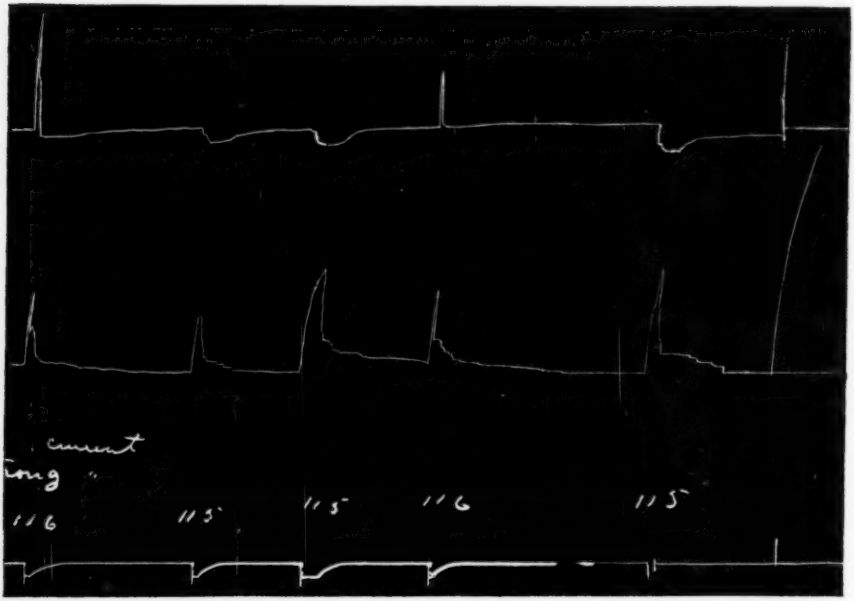

Fig. 15.—Sherrington preparation. Reciprocal innervation observed upon a reflex elicited by electrical stimulation of a contralateral cutaneous sensory nerve (115). When a strong stimulus was applied, co-contraction resulted (116). Upper tracing is tibialis anticus tendon; lower tracing is gastrocnemius tendon.

simultaneous relaxation in the biceps. This reaction is similar to the preceding one, and illustrates the effect of phasic reflexes upon tonic ones (fig. 14).

Reciprocal innervation was constantly observed in contralateral reflexes elicited by electrical stimulation of a sensory cutaneous nerve; but when a strong current was used co-contraction occurred in the same muscle preparation (fig. 15). Similar reciprocal innervation

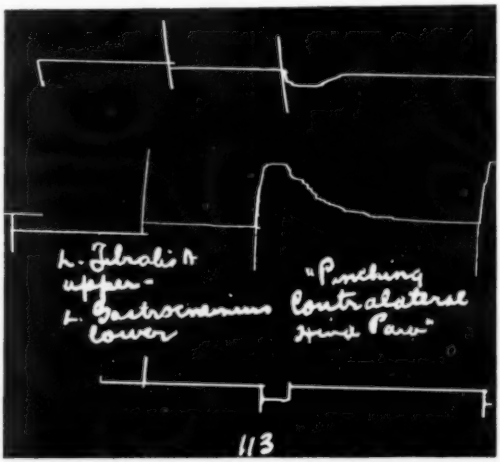

FIG. 16.—Reciprocal innervation elicited by pinching contralateral hind-paw in a Sherrington preparation.

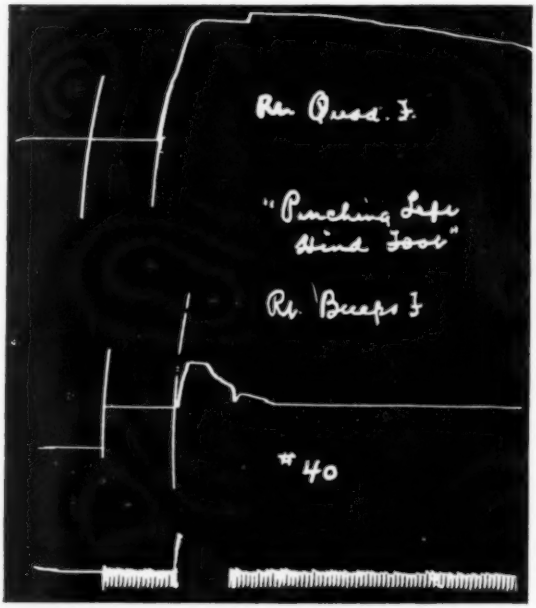

FIG. 17.—Co-contraction elicited by pinching contralateral hind-paw in an anæmic decerebrate animal which showed extreme extensor tone.

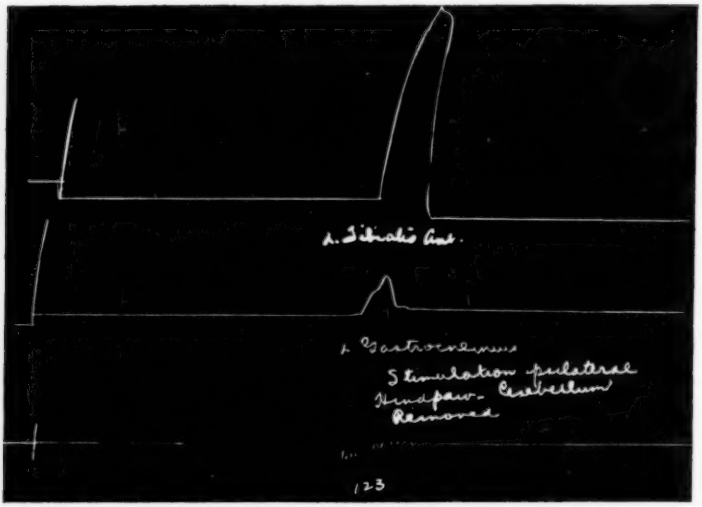

FIG. 18.—Sherrington preparation with the cerebellum removed. Co-contraction elicited by electrical stimulation of ipsilateral hind-paw.

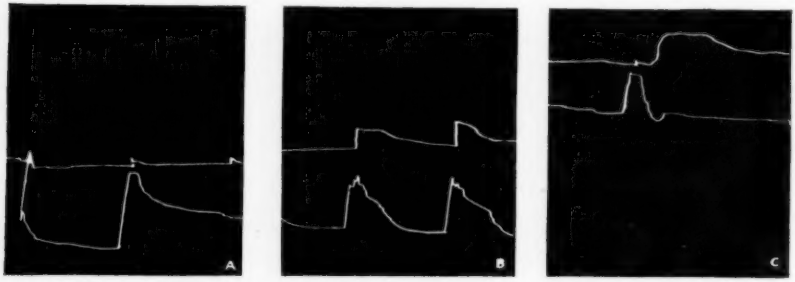

FIG. 19.—A, Co-contraction elicited by pinching medial side of ipsilateral paw in an anæmic decerebro-cerebellate animal.

B, Increase of contraction of gastrocnemius with co-contraction elicited by pinching lateral side of ipsilateral paw in same animal.

C, Reciprocal innervation producing contraction of gastrocnemius when the tibialis anticus relaxed following a contraction resulting from ipsilateral pinching of paw with flexor tone predominating in same animal. Upper tracing is gastrocnemius tendon; lower tracing is tibialis anticus tendon.

resulted from pinching the contralateral paw (fig. 16), but when a preparation showed extreme extensor tone in some instances co-contraction occurred (fig. 17).

Removal of the cerebellum produced no change in the functional relation of antagonistic muscles, nor in the character of the reflex patterns. Co-contraction occurred in reflexes elicited by ipsilateral nociceptive stimuli (fig. 18). When the medial side of the paw was pinched the tibialis anticus showed a marked contraction, whereas the gastrocnemius showed a small one (fig. 19A); when now the lateral side was pinched the amplitude in the gastrocnemius was increased (fig. 19B). If the head was turned vertex up so that flexor tone predominated, then very slight contraction occurred in the gastrocnemius, and when the tibialis anticus relaxed an increment of tone was seen in the gastrocnemius (fig. 19C).

Co-contraction and reciprocal innervation both occurred as the result of reflex activity depending upon the particular function to be served. Schoen [21], in describing the "*Stützreaktion*" in the fore-legs, noted simultaneous contraction of antagonistic muscles when fixation of joints was the purpose of the reflex. Pritchard [22], describing the same reflex in the hind-legs, showed that when stretching alone was the purpose, reciprocal innervation occurred.

Summary.

(1) Ipsilateral nociceptive stimuli produced co-contraction in spinal, decerebrate and decerebro-cerebellate animals.

(2) Contralateral nociceptive stimuli produced reciprocal innervation, except when very strong stimuli were used, or when the muscle opposed to that one whose contraction the reflex evoked was in a state of heightened tone.

(3) Non-tonic reflexes from the neck accompanying tonic ones produced a simultaneous contraction in the antagonistic muscle, which immediately relaxed and continued to relax during the heightened tone of the agonist.

(4) Phasic reflexes inhibiting tonic ones produced reciprocal innervation.

(5) The distribution of tone, as modified by neck and labyrinthine reflexes, determined the degree of functional inter-relation of muscle contractions produced by phasic reflexes, and at times prevented any activity in the opposing muscles.

(6) When co-contraction occurred as the result of an ipsilateral nociceptive stimulus, and the increase in tone was sustained by a tonic reflex in one of the muscles, the antagonist contracted as that muscle relaxed.

(7) Removal of the cerebellum did not affect the functional interrelation of muscular contractions resulting from tonic and certain phasic reflexes.

It is evident that these observations cannot be used to determine the behaviour of antagonistic muscles in voluntary movements.

Chapter VI.—Influence of Removal of the Cerebellum upon the Tonic Labyrinthine Reflex. Opisthotonos.

In conformity with the work of others, our observations have thus far shown that removal of the cerebellum has no effect upon the development, degree and distribution of decerebrate rigidity. Magnus [23] pointed out the pertinent fact that "we know not a single function or reflex positively connected with the cerebellum, in such way that it is absent after cerebellar extirpation, and present after ablation of other parts of the brain, as long as the cerebellum remains uninjured." Elsewhere [24] he states that "at some time it is likely that it will be shown that impulses from the cerebellum travelling to the brain-stem centres either inhibit or augment labyrinthine reflexes." In support of this he quotes the work of Bauer and Leidler, in which destruction of the vermis was followed by an increase of the "*Augendrehreaktion.*"

We propose to show that the cerebellum as a whole inhibits in a general way tonic labyrinthine reflexes.

In a communication read before the Association for Research in Nervous and Mental Diseases, in December, 1926, we reported some observations upon twenty-five animals decerebrated by the anæmic method. Animals decerebrated by a saw or guillotine were found unsuitable for this study, because of the resulting hæmorrhage and shock. The cerebellum was removed piecemeal, or in most instances the inferior cerebellar arteries were either tied, electro-coagulated, or severed. The superior cerebellar arteries were already anæmic because of the ligatures placed upon the basilar and carotid arteries. The results were uniform in all animals.

Such a decerebrc-cerebellate animal showed a continuous persistence of the rigidity produced by the anæmic decerebration. Labyrinthine

and tonic neck reflexes were present. If the head of an ordinary decerebrate animal lying on its side was turned vertex down, an increase of tone in the outstretched extremities rather slowly and smoothly ensued until the optimum of extensor rigidity was produced. If the head of a decerebro-cerebellate animal was turned vertex down, the fore-legs were thrust forward suddenly with great force and with unsheathing of the claws. The force of this tonic contraction was so great that often the whole body was displaced. Its sudden appearance was tetanic, startling and entirely dissimilar to anything observed in an ordinary decerebrate preparation. The rigidity in the extremities was so marked that passive flexion could be performed only by the greatest force (fig. 20).

Immediately following removal of the cerebellum the head

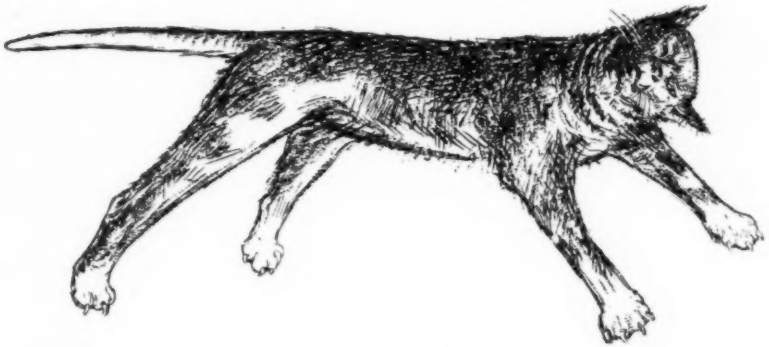

FIG. 20.—Exaggerated labyrinthine tonic reflex in a decerebro-cerebellate animal.

assumed an attitude of extreme opisthotonos. If it was passively flexed the rigidity in the extremities, the fore-legs especially, diminished and a position of semiflexion was assumed. If the head was released, it slowly assumed the original position of opisthotonos with accompanying extreme extension of the fore-legs. If the animal was then turned on its back, the markedly retracted head rested on its frontal pole and the chin was in a line extended from the neck. The animal could then be balanced in this position, which would be retained indefinitely. If placed upon its abdomen with the extended fore-legs hanging over the edge of the table, the marked retraction of the head persisted unchanged (fig. 21).

Extreme opisthotonos has been described by Bazett and Penfield [25] in certain decerebrate animals immediately after operation, and was generally accompanied by tonic fits in which the rigidity underwent extreme accentuation. In these animals the respiration was usually slow, though occasionally there was a fast and shallow respiration. Bazett and Penfield say that this condition is seen in animals with evidence of post-operative hæmorrhage, and that as a rule blood is found below the tentorium.

The degree of opisthotonos which we have described in decerebro-cerebellate animals has never been observed by us in ordinary decerebrate animals. It was not due to hæmorrhage or other injury to subtentorial

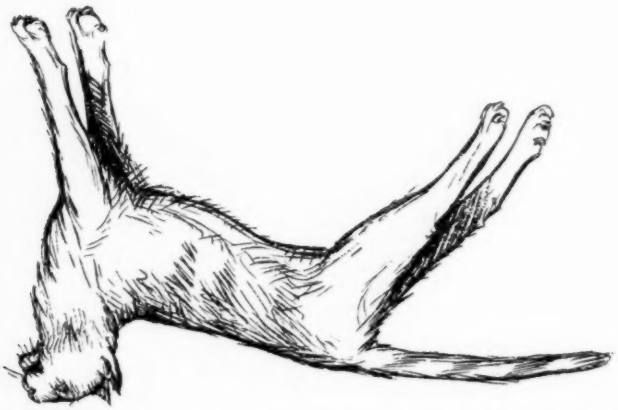

FIG. 21.—Opisthotonos resulting from removal of cerebellum in a decerebrate animal.

structures, as will be seen from the following observation. When the labyrinths were destroyed in such an animal the opisthotonos entirely disappeared. Of course, tonic labyrinthine reflexes were absent. From this we conclude that the cerebellum as a whole inhibits tonic labyrinthine reflexes which are responsible for the production of the marked increase in rigidity when the head is turned vertex down and for the extreme opisthotonos.

Our results, therefore, offer an explanation of the inhibition of decerebrate rigidity found by some investigators upon stimulation of the cerebellar cortex, underlying structures, or the superior cerebellar peduncles. Sherrington [26], Miller and Banting [27], Cobb, Bailey and Holtz [28].

Chapter VII.—Influence of Removal of the Cerebellum and of Decerebration immediately below the Inferior Cerebellar Arteries upon Rebound Extension and the Scratch Reflex.

Twenty-four other decerebrated animals and with the cerebellum removed by the anæmic method, and thirty animals in which the decerebration was made by ligating the basilar artery immediately below the inferior cerebellar arteries, thus rendering the whole cerebellum functionless, were studied. The former animals have already been described. The latter differed in certain respects. Labyrinthine tonic reflexes were less frequently encountered; tonic neck reflexes were elicited constantly. Decerebrate rigidity in extension was present and remained unimpaired in some animals for thirty-six hours. Many animals died of respiratory failure after one or two hours. Vomiting and respiratory difficulties were common.

None of the reflex activities showed any difference from those found in the ordinary decerebrate animal with an intact cerebellum, or from those found in animals decerebrated immediately above the inferior cerebellar arteries.

Rebound extension.—When a hind-leg of a suitable preparation was pinched briefly and released, a flexion reflex occurred followed by an extremely vigorous kick. The rebound was far greater than had been observed in ordinary decerebrate animals. Not only was there an increase in the facility with which this was elicited and of vigour, but continued gentle pressure of both hind-paws produced rhythmic rebounds so strong that the animal literally kicked itself off the table. Rebound extension of the fore-leg was obtained only in the first type of preparation, and the movement resembled a clawing or striking.

Scratch reflexes.—Stimulation of the external auditory canal, at times the nostrils and even about the mouth, evoked a strong and sustained scratch reflex of the ipsilateral hind-leg, which would be inhibited by nociceptive and tonic neck reflexes.

Sherrington [29] has shown that inhibitory depression of spinal motor centres is followed on removal of the inhibition by a state of activity greater than that obtaining in them before inhibition. "This post-inhibitory exaltation manifests itself not only by increased responsiveness to stimuli externally applied; its gives also the 'rebound extensions' which follow on reflex flexion when the stimulus for the latter is withdrawn. In decerebrate and spinal reactions the with-

drawal of a flexion stimulus is commonly followed by an active extension. Thus, a brief nociceptive flexion reflex is in the decerebrate preparation generally diphasic, active extension following as a rebound on the flexion when the external stimulus is withdrawn." In the decapitated or spinal animal the rebound extensions are less common and less vigorous, but they occur. On the other hand, the rhythmic reflex of alternating flexion and extension which constitutes the scratch reflex is more readily elicitable in the decapitated or spinal preparation than in the decerebrate animal.

Rebound extensions are found to be more common and more vigorous in two types of preparations; in animals decerebrated at the usual level (fifth cranial nerve) with their cerebellum removed, and in animals decerebrated immediately below the inferior cerebellar arteries. In the former preparations the rebound extensions occurred chiefly in the hind-legs. When the labyrinths were removed in a decerebrate animal, marked rebound extension occurred in the fore-legs in the pattern of a clawing movement. It should be recalled that when in a decerebrate animal the labyrinths are destroyed and the head allowed to fall into a flexed position, only the fore-legs are persistently flexed; the hind-legs are strongly extended. The distribution of extensor tone into the fore- and hind-legs is mediated by different mechanisms. The former probably is related more to the labyrinth; the latter to the reticulo-spinal formation.

Although it has been stated by Walshe that the force of the rebound and the degree of exaltation will depend upon the intensity of extensor tone originally present, it seems probable that the force and frequency of the rebound extension in the fore-legs is not dependent entirely upon the degree of extensor rigidity, but is more likely due to the suddenness, rapidity and force of the flexion reflex. Thus, in ordinary decerebrate animals, when a sustained flexion was produced by long-lasting stimulation, a rebound extension was rare. In the labyrinthineless animal flexor patterns were more easily evoked, and the resulting reflex was more rapid and pronounced.

In our earlier experiments, when we were concerned with the development of the technique of the anæmic method of decerebration, we described an acute decerebrate preparation [30]. In this description we stated that "stimulating the auditory canal will produce a shaking of the head, movement of the ear, and a scratch movement of the ipsilateral hind-leg. At times this scratch movement may be evoked from stimulation about the mouth, nose and throat, and occa-

sionally it seemingly may occur spontaneously." Although this is true of some animals decerebrated at the ordinary level, a review of our protocols showed that we failed to note that when the scratch reflex occurred in such a preparation, usually the animal was not in good condition, either because of faulty technique or long duration of the decerebrate rigidity, or that the rigidity was not as marked as usual. On the other hand, the reflex was common in such animals as were decerebrated immediately below the inferior cerebellar arteries. Of these a considerable number were recorded, but at that time we were not concerned with levels of decerebration.

Reviewing all of our records, we are of the opinion that the scratch reflex occurs much less frequently and is far less sustained and vigorous in animals decerebrated at the ordinary level than below the inferior cerebellar arteries. Sherrington [31] has pointed out that the decerebrate preparation may be described as exhibiting less tendency to develop a refractory phase under the continuance of a stimulus. The tendency is especially marked when, as happens in the great majority of cases, the decerebrate preparation presents its characteristic extensor rigidity. Despite the existence of good extensor rigidity, the animals decerebrated immediately below the inferior cerebellar arteries showed a constant development of a refractory phase under the continuance of a stimulus, as contrasted to those decerebrated immediately above the inferior cerebellar arteries. It is apparent that the extensor rigidity of decerebrate preparations is not the only factor which prevents the development of a refractory phase under the continuance of a stimulus, and it is probable that removal of the cerebellum in such a preparation permits its development. The co-existence of good decerebrate rigidity, rebound extension and rhythmic reflexes points to the likelihood that it is not the extensor rigidity alone which prevents the development of a refractory phase.

More constant and more vigorous rebound extension and scratch reflexes occurred following a decerebration immediately below the inferior cerebellar arteries as contrasted with one immediately above. The only structure which was rendered functionless was the remaining part of the cerebellum and vestibular nuclei. Some of the dorsal and ventral spino-cerebellar tracts and the vestibular nuclei, as well as the inferior portion of the cerebellum, were supplied with blood in the former preparation. Destruction of the labyrinths in a decerebrate animal does not increase the frequency or vigour of the scratch reflex. It is, of course, possible that afferent stimuli coming up the direct

cerebellar tracts may play upon the vestibular nuclei, either directly or by way of the roof nuclei and fastigio-vestibular tracts, and influence tonic postural reflexes by way of the vestibulo-spinal tracts.

Graham Brown has shown that heightened tone of the neck musculature produced an exaltation of the receptor zone of the scratch reflex. It is possible in this case that the heightened tone is the result of removal of cerebellar inhibition, as was the case with the labyrinthine tonic reflex.

Chapter VIII.—Theoretical Discussion.

It is logical to expect that the cerebellum may have but little relation to the functions of a decerebrate animal, which possesses, in addition to the spinal reflexes, only a limited number of postural reflexes, which are formed into definite and constant patterns which may be released by suitable stimuli. It is not surprising to find that those reflex patterns are integrated in the brain-stem and not in the newer-formed cerebellum. The influence of the cerebellum upon such reflex patterns would theoretically be assumed to consist only of their inhibition or exaltation. When the cerebellum is removed in an animal possessing an otherwise intact central nervous system, the defects in function are marked and manifold, as may be expected from the assumption that as the newer-formed cerebrum and cerebellum develop they are concerned with the utilization and direction of lower reflex patterns and of voluntary movement. The complexity of postural and phasic activity is such that no crucial experiment has been devised which presents any conclusive proof of the mechanism of cerebellar function. Only such parts of its function as are related to more simple reflex activities have thus far lent themselves to critical analysis.

Rademaker [32] has shown that strong "*Stütztonus*" (supporting tone), active uninhibited static reactions (magnet, *Stütz*, etc.), and active uninhibited labyrinthine and righting reflexes occur in cerebellumless animals. Although he was unable to explain the genesis of cerebellar ataxia, it is his belief that the removal of inhibition as expressed in the facility of evoking the above postural reflexes and their increased force played an important rôle in the production of dysmetria.

It is of some interest and importance that he found in otherwise intact animals, as we did in decerebrate animals, that destruction of the cerebellum removed some inhibition to certain postural reflex activities, some of them common to both preparations (labyrinthine reflexes).

The inhibitory function of the cerebellum upon certain postural activities residing in the brain-stem of a decerebrate animal probably is but a very small part of its activity, and may be a relatively unimportant one. Certainly no generalization can be made from this as to its possible function in relation to higher cerebral activities. Further research, incorporating this fraction of functional activity with stimulations and ablations of higher cerebral levels, may point to an elucidation of the unsolved problem of cerebellar function.

Chapter IX.—Conclusions.

(1) The pattern and degree of rigidity in a decerebrate animal is not changed by removal of the cerebellum.

(2) Lasting patterns of rigidity in flexion occur in labyrinthineless decerebrate animals and are unchanged by removal of the cerebellum.

(3) Co-existing normally distributed tone, patterns of rigidity in extension and flexion, crawling, climbing and springing are produced in animals in which a segment of the basilar artery has been isolated between two ligatures some distance apart, and in animals decerebrated at a relatively high level. Removal of the cerebellum does not affect the pattern or degree of these activities.

(4) Removal of the cerebellum does not affect the functional interrelation of muscular contractions resulting from tonic and certain phasic reflexes of a decerebrate animal.

(5) The cerebellum as a whole inhibits in a general way the tonic labyrinthine reflexes.

(6) The cerebellum inhibits rebound extensions in a decerebrate animal.

(7) Removal of the cerebellum permits the regular and forceful occurrence of rhythmic reflexes in a decerebrate animal.

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(4) EXPERIMENTAL INVESTIGATIONS ON THE CEREBELLUM.

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AT a meeting of the Neurological Society of London, forty years ago, Dr. Hughlings Jackson took part in the discussion of a paper on "Muscular Hypertonicity in Paralysis." In the course of his remarks some notable views on cerebellar function were expressed, which I believe will be of general interest to have recalled [12]: "I submit that the cerebrum represents all parts of the body, and that the cerebellum also represents all parts of the body. But the two representations are in inverse order; putting it roughly and neglecting some parts, the cerebral order is arm, leg, trunk. This is admitted when we say that the brain is the organ of volition, for the order stated is the order of the parts as they are most often used voluntarily. The cerebellar order of representation is the opposite—trunk, leg, arm. This is admitted by those who say that the cerebellum is the organ of co-ordinating locomotor movements, for that expression only means an organ where muscles of all parts of the body are represented in complex ways. The order of getting parts into play in locomotion, from walking to swift running, is trunk, leg, arm."

The extraordinary clearness of these conclusions which had been arrived at by clinical observation and deduction, are the more remarkable when it is remembered that they were made at a time when there was great confusion in regard to cerebellar anatomy. Though new cerebellar associations were being reported from time to time, they were as often denied, yet Jackson pursued his own line of reasoning which led him eventually to the belief that the cerebellum was the essential organ in locomotion and progression. Consequently it was necessary to have associated ocular movements represented; and to provide for all this it was indispensable that the cerebellar cortex should be the first chief station of representation of the afferent impulses from all parts of the body.

In referring to these remarks it is interesting to observe how our increasing knowledge of cerebellar anatomy has so abundantly supported them.

In the following experimental investigations on the afferent (and efferent) connections of the cerebellum some additional tracts will be described by which "muscles of all parts of the body may be represented in the cerebellar cortex"; and in the results of cortical stimulation of the cerebellum the "complex manner of this representation with associated ocular movements" will be indicated.

The results of this research, which also includes the red nuclei and the flocculus, will be considered under the following subdivisions:—

(I) The cerebellar connections of the posterior column nuclei of Goll and Burdach, and of the tubercle of Rolando.

(II) The cerebellar nuclei and their associations.
- (*a*) The nuclei considered from an experimental standpoint.
- (*b*) The connections of the median group, the nuclei of the roof and the globosus.
- (*c*) The response of the posterior vermis and the median nuclear group to stimulation.
- (*d*) The anatomical relations between the posterior vermis and the median group of nuclei.
- (*e*) The connections of the lateral group, the nucleus dentatus and emboliformis.

(III) The red nucleus in the cerebeller arc, with a criticism of the conclusions of Magnus and De Klejn.

(IV) The flocculus.

(V) A preliminary report on the response of the cerebellar cortex to stimulation.

(I) The Cerebellar Connections of the Posterior Column Nuclei, and the Sensory Nucleus of Rolando.

The nuclei of Goll and Burdach and the tubercle of Rolando act as central receiving and relaying stations for sensory impressions from the entire body. The impulses from the legs and lower trunk pass to the nucleus gracilis; the nucleus cuneatus serves the upper trunk, arms and neck; while the tubercle of Rolando is concerned with the impulses received from the head.

The course of the fibres which arise in these nuclei has been the subject of investigation for many years. Amongst the earliest to give attention to this problem was Flechsig [7], who in 1881, working by the myelinization method, claimed that all of the fibres from these nuclei entered the median lemniscus. Some of these he traced to their ending in the thalamus, others he followed through the internal capsule to the

sensory cortex of the cerebrum. No mention is made of any fibres going to the cerebellum, but a few years later he considered it very probable that the cerebellum did also receive some fibres from these nuclei. This latter observation was denied by von Vejas [27] in the same year.

Then von Monakow [16] reported that some of the fibres of the posterior column nuclei were distributed to the cerebellum through the corpus restiforme, and claimed that these arose from the lateral nucleus of the funiculus cuneatus. This view was later supported by Blumenau, but in neither case was the distribution of the fibres mentioned.

Ferrier and Turner (1894) in their experiments found degeneration in the corpus restiforme on the side of lesion only [6]. And the investigations of Mott (1895) and Risien Russell (1897) had to do chiefly with the median fillet, no mention being made of any fibres going to the cerebellum.

The following year (1898) Tschermak [25] made lesions in the nuclei of the dorsal funiculi and described four systems of fibres: (1) A crossed system forming the median fillet which proceeds to the thalamus; (2) a crossed system which runs partly in the median fillet to the thalamus, and partly to the sensory cortex; (3) a crossed system of external arcuate fibres through the corpus restiforme to the cerebellum; (4) an uncrossed system through the corpus restiforme to the cerebellum.

In 1902 Probst [18] destroyed the posterior column nuclei on one side in dogs and cats, and traced the degenerations through the corpus restiforme on the same side to the cortex of the superior vermis. He also described fibres to the nucleus of Deiters on the same side.

Then Lewandowsky in 1904 [13] and Horsley in 1906 [10] denied that the cerebellum received any fibres from the nuclei of the posterior columns. And their conclusions would seem to have been in agreement with the generally accepted view of that time, that all sensory impressions were conveyed to the thalamus. But in the same year van Gehuchten's researches [8] added some support to Tschermak's claim that the cerebellum did receive fibres from the posterior column nuclei; though he qualified this by stating that it was only through the dorsal external arcuate fibres.

Since then, the view that the dorsal nuclei do send fibres both direct and crossed to the cerebellum has been generally accepted, and has the approval of the more recent authorities—Winkler [28], Ranson [19], Tilney and Riley [24].

But if these conclusions are to be taken as final, then the relationship between the posterior column nuclei and the cerebellum would be far from satisfactory, for the termination of all these fibres is considered to be the anterior vermis. In fact the only connections so far described

between the spinal cord and the posterior vermis are the few fibres of the dorsal spino-cerebellar tract mentioned by Ingvar [11] and Beck [2]. It is unbelievable that this large posterior region of the vermis, containing folia which are in relation to the movements of the head and eyes, and certain correlated activities in the body musculature, should not be more closely associated with the nuclei of the dorsal columns of the spinal cord. Believing that other connections from the posterior column nuclei probably existed, it was decided to reopen this question in the hope that with a greatly improved Marchi technique some interesting and possibly conclusive results might be found.

In the cat the nuclei of Goll and Burdach are represented by two elongated groups of cells approximately 8 mm. in length and 2 to 3 mm. in breadth where they extend slightly above the level of the obex. An

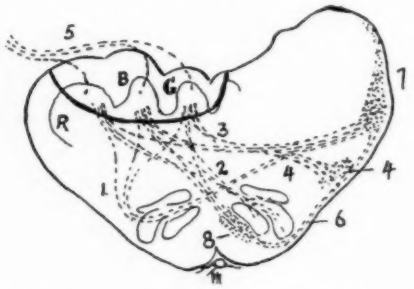

FIG. 1.—Diagram of a transverse section through the medulla oblongata at the level of the posterior column nuclei. The heavy line marks the approximate extent of the lesion which involved the nuclei of Goll (G), Burdach (B), and the median half of the tubercle of Rolando (R). The following degenerated fibre groups are shown: 1, Direct arcuato-olivo-cerebellar; 2, crossed arcuato-olivo-cerebellar; 3, transverse arcuato-restiform; 4, transverse arcuato-extrarestiform; 5, dorsal arcuato-restiform; 6, ventral arcuato-restiform; 7, restiform body; 8, median fillet.

attempt was made by means of a fine thermo-cautery to destroy these nuclei—in some cases throughout their entire extent, in others the caudal or oral portions—in order that as great a mass of degeneration as possible would result. For in some of the earlier experiments, made by transverse section through the nuclei, a comparatively small number of cells were destroyed, which resulted in so fine a degeneration that it was difficult to follow; and though an attempt was made to limit the destruction to one or other of the nuclei, the sections always showed, as previous investigators have remarked, that the neighbouring nuclei were also partially damaged. In one of these experiments in which the degenerated area involved the nuclei of Goll, Burdach, and the tubercle of Rolando, several definite groups of fibres were found. Besides the

well-known dorsal and ventral arcuate fibres which run to the restiform bodies and the fillet, five other fibre groups could be observed (fig. 1).

(1) The direct arcuato-olivo-cerebellar fibres which enter the lateral region of the inferior olive of the same side, to pass out by the hilus, probably giving off collaterals *en route*. Then taking a dorsolateral direction they enter the opposite restiform body.

(2) The crossed arcuato-olivo-cerebellar fibres, which enter the opposite inferior olive through the hilus, to be distributed to the cells of this nucleus.

(3) Transverse arcuato-restiform fibres which cross the median line directly to enter the restiform body.

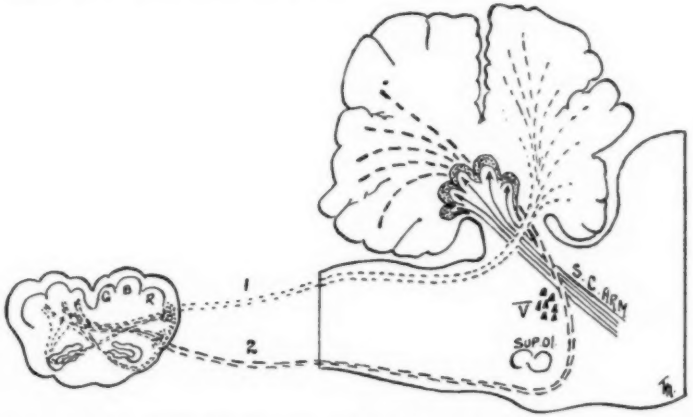

FIG. 2.—Diagram illustrating the course and distribution of the arcuato-cerebellar fibres: 1, The arcuato-restiform fibres maintain a dorsal position in the oblongata, and passing lateral to the superior cerebellar arm are distributed to the anterior vermis; 2, the arcuato-extrarestiform fibres follow the ventral course taken by Gowers' tract; at the level of the superior olive they turn dorsally and passing anterior to the motor fifth, and lateral to the superior cerebellar arm, they enter the cerebellum to be distributed to the posterior vermis.

(4) Transverse arcuato-extrarestiform fibres, which cross directly to form a compact bundle in the ventrolateral region of the medulla.

(5) Mesial fillet collaterals to the cerebellum by way of the superior cerebellar arm.

We thus have possibly five connections from the dorsal sensory nuclei and the tubercle of Rolando that have not been previously described. The fibres which pass through the inferior olives will be considered in a later communication. At present the two tracts which cross the oblongata transversely, and the collaterals from the mesial fillet, will be dealt with, as they probably play an important rôle in relation to the cortical reactions of the vermis.

Owing to the diffuse character of the lesions it is only possible to surmise that these two groups of transverse fibres arise from the cells of the nuclei of Goll, Burdach, the nucleus of v. Monakow, and possibly

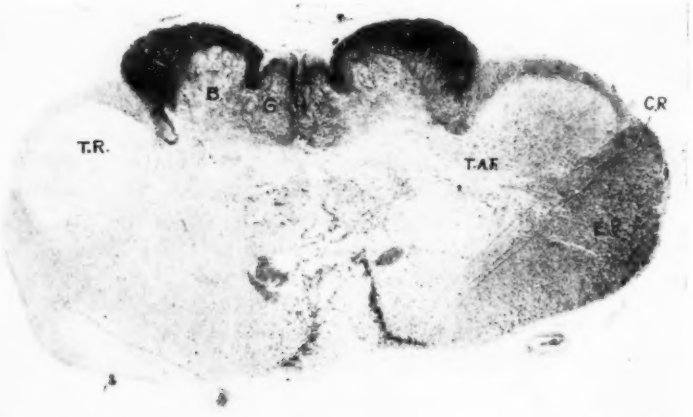

FIG. 3.—The oblongata above the lesion after injury of the nuclei of Goll and Burdach. Degenerations in and around the nuclei of Goll and Burdach, principally on the left side. A number of transverse arcuate fibres (T.A.F.) pass to restiform body (C.R.) and to the ventrolateral region, to form the extrarestiform bundle to the cerebellum (E.R.). No definite grouping of the fibres in Gowers' or Flechsig's tract is found.

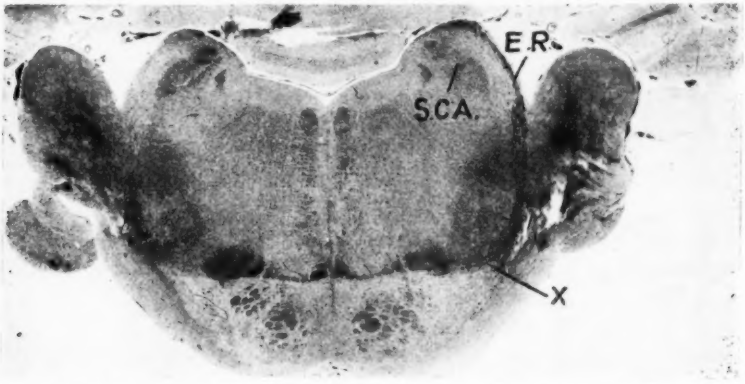

FIG. 4.—Extrarestiform fibres (E.R.) passing dorsally to enter the cerebellum over the S.C. arm. From the degenerated median lemniscus on the right side a few fibres are seen to pass laterally to join the previously mentioned group (E.R.).

in part from the tubercle of Rolando. They cross the median line transversely and then divide into a dorsal portion, the transverse arcuato-restiform fibres, which enter the restiform body; and a ventral portion

which from its course has been called the transverse arcuato-extra-restiform tract (figs. 1-5)—which occupies the same ventrolateral region of the oblongata in which the fibres of Gowers' tract are found. And like Gowers' tract these fibres run along the ventrolateral surface of the stem of the hind-brain to the level of the superior olive. Here they turn dorsally, and after hooking over the root of the fifth nerve proceed to the superior cerebellar arm over which they swing medially to enter the cerebellum some distance from the inner side of the fibres of the restiform body. Some of the fibres are then distributed to the roof nuclei on both sides, the remainder passing posteriorly to terminate in

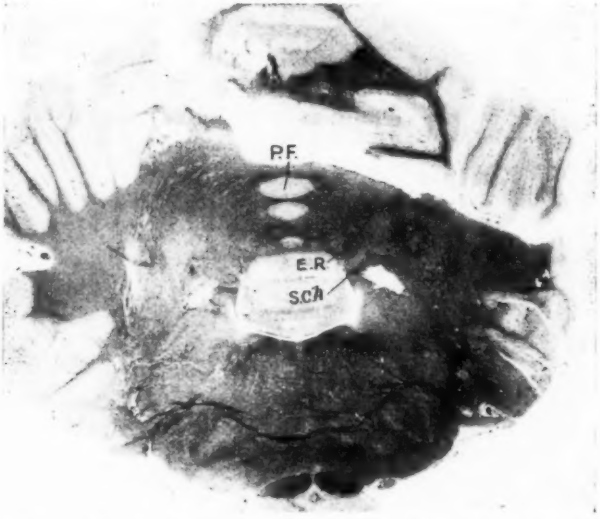

FIG. 5.—The E.R.F. leaving the median surface of S.C.A. to the roof nuclei, posterior to the primary fissure (P.F.). The restiform fibres are shown laterally as they pass forward to the anterior vermis.

the pyramis lobule of the vermis. The fact that these two sets of fibres are so clearly separated and take such different paths, for they cross almost at right-angles on the lateral surface of the superior cerebellar peduncle, makes it easily possible to follow them to their terminations. As will be seen later, these fibres form an important link between the contralateral spinal cord and the cerebellum, and will help us better to understand the reaction of the head and eyes when the posterior vermis is stimulated.

The transverse arcuato-restiform fibres (1, fig. 2), having united with the other groups of degeneration, pass through the inferior cerebellar arm

to be distributed to the anterior vermis. Thus the afferent impressions from the posterior column nuclei and the tubercle of Rolando are conveyed to both the anterior and posterior lobes of the vermis, and there is clear evidence to support the view that these fibres are distributed to both sides.

In the same series in which the above fibres have been described another and much smaller group has been observed. These are collaterals which are given off from the median lemniscus at the level of the superior olives. After reaching the lateral surface of the oblongata they swing dorsally to join the previously mentioned group of extrarestiform fibres to the cerebellum. These collaterals are found in every series in which the median lemniscus shows a well-marked degeneration. And it appears to be generally the coarser fibres which pass by the superior cerebellar arm to the posterior vermis, the finer fibres continuing to the thalamus. This would be in agreement with Blumenau's observation by the Golgi method, that it is the axis cylinders from the large cells (of the nucleus cuneatus) that run to the cerebellum (fig 4.)

In regard to the transverse arcuato-restiform and the extrarestiform fibres the question will naturally arise as to why they are considered to belong to the posterior column nuclei, and not to Gowers' and Flechsig's tracts which their position and course suggest. After a careful examination of the sections in which their origin, course and termination have been followed, the possibility of their belonging to either of the spino-cerebellar systems has been eliminated on the following grounds. In the first place the lesion was intended to destroy only the nuclei of Goll and Burdach, and though unfortunately the sections containing the lesion are missing, the extent of the destruction can be clearly determined by the degeneration observed in the cervical cord and in the medulla. If the destruction had been so extensive as to involve the right ventrolateral region, both the rubrospinal and the crossed pyramidal tracts would have been injured and a dense degeneration in the dorsolateral region of the cervical cord would have resulted. But here we find only a scattered degeneration in the area occupied by the crossed pyramidal tract, which very probably resulted from injury to some of the fibres in the pyramidal decussation. In addition to this, if the tracts of Gowers and Flechsig had been destroyed there would be a very definite grouping of their fibres above the lesion, instead of which the Marchi-stained sections show only a diffuse degeneration. And finally, the evidence indicates that these fibres terminate in the posterior vermis, while it is generally agreed that Gowers' tract is distributed to the anterior vermis.

In experimental work, when some unusual feature is observed it seems

only proper that it should be reported, even though proof may be lacking. So these extrarestiform fibres from the posterior column nuclei have been presented for consideration, realizing that some doubt as to their origin exists, but with the belief that future work in this field will confirm the observations.

As to the function of the nuclei of the dorsal funiculi many conflicting reports have been made. Ferrier and Turner [6] in their researches on monkeys found that after injury of these nuclei there was restlessness, sprawling of the body on exertion, and a tendency to fall backwards. The sensation to touch, pain and localization appeared unimpaired, and the disturbance in equilibrium disappeared in a few days. Von Bechterew's dogs tumbled about on walking and swayed on standing [4]. He also reported cutaneous sensation to be unimpaired.

Tschermak's cats showed at first marked disturbance in equilibrium, which soon disappeared [25]. On attempting to walk they deviated toward the side of the lesion, and often fell when using the paw of the affected side. And while the contralateral fore-paw was almost normal, the homolateral leg sprawled about on attempting to use it. Cutaneous sensation was not disturbed.

It will be observed that in each of these investigations three important facts were mentioned. Von Bechterew's dogs tumbled on walking; the monkeys of Ferrier and Turner sprawled; and Tschermak's cats fell when using the affected paw; that is to say, in all these animals there was evidently a marked disturbance in the postural sense of the leg or legs affected. The disturbance in equilibrium might have been due to interference with the cerebellar connections from the posterior column nuclei, or, what is more probable, to injury of the spino-cerebellar tracts. In each series cutaneous sensation was normal.

In my investigations the characteristic symptom was a loss of the postural sense in a joint, limb or limbs. Pain and temperature always appeared to be normal and equilibrium was but slightly disturbed, probably owing to the small size of the lesion. In Experiment 62, which is a very good example, the nuclei of Goll and Burdach were cauterized on the right side. The loss of sense of position in the right fore-leg was well shown, the foot being turned under while the animal was quietly resting on its dorsal surface. The shoulder was affected to a less extent. From the position of the hind-legs it appeared that they were also abnormal, but any awkward position into which they might be placed would be at once corrected. This was also the case with the left fore-leg. Of some importance is the fact that the loss of sense of position in this and other cases did not recover at the end of three weeks.

From these experiments it has been clearly demonstrated that the function of the posterior column nuclei is to convey afferent impressions from the muscles, tendons, and joints of the entire body to the cerebellar vermis and the opposite thalamus. And when it is considered that each folium of the vermis forms part of a definite synergic unit, the whole of which appears in some instances to be composed of the group of folia comprising the particular lobe, e.g., the posterior vermis and the lobus centralis, the necessity of each folium receiving these afferent impressions will be realized. For only in this manner could a balance be maintained between the agonists and the antagonists, and provision made for correlating the associated muscular reactions of the limbs with the body, without which the integrative synergic activity of the cerebellum would be impossible.

(II) The Cerebellar Nuclei and their Connections.

(*a*) *The Nuclei considered from the Experimental Standpoint.*

Probably the first to give a detailed description of the central grey masses of the cerebellum was Stilling [22], who in 1874 described the nuclei by the terms : Dachkern, Kugelkern, Pfropf, and corpus dentatum. In a beautifully finished plate of a horizontal section through the cerebellum the relative size, position and arrangement of these nuclei are shown.

Since that time it appears to have been generally accepted that there are four distinct nuclear masses, though neither anatomically nor histologically has any clear reason been advanced in support of this belief ; while against it is the obvious fact that if the nuclei are examined through a complete series it will be observed that the two median nuclei merge together, and that the two lateral are inseparably connected. Nevertheless many theories regarding the separate connections of these nuclei have been proposed, one of the most recent being that described by Marburg [15], according to which the roof nucleus gives origin to the hook bundle which is mentioned as terminating in the vestibular nucleus ; the globosus and emboliformis are considered to send their fibres to the nucleus magnocellularis of the red nucleus, while the fibres of the nucleus dentatus run in part to the nucleus parvocellularis and in part to the thalamus.

As these views are founded on human pathology and experimental results following gross lesions in animals, they are not very reliable. How they compare with the degenerations arising from minute lesions directly in the nuclei will be considered in the discussion of the experiments.

In the following investigations the objective was to determine the relationship of these nuclei to each other, and their associations with the hind-brain, mid-brain, and thalamus. With Clarke's stereotaxic instrument a number of small lesions were made in the individual nuclei of different animals. In the accompanying table the results have been briefly summarized :—

EXPERIMENTAL LESIONS OF THE CEREBELLAR NUCLEI.

Medium group		Lateral group		Degenerations				
Roof	Globosus	Emboli-formis	Dentate	Hook bundle	Fastigio-Deiters	Superior cerebellar arm.	Red nucleus	Thalamus
Yes	?	—	—	Yes	Yes	—	—	—
,,	Yes	Slight	—	,,	,,	To decus.	—	—
,,	,,	,,	—	,,	,,	Slight	Slight	Slight
Slight	,,	,,	—	Slight	Slight	,,	,,	,,
—	—	Yes	—	—	—	Medium	Medium	Medium
—	—	—	Yes	—	—	,,	,,	,,
—	—	Yes, dorsal	Dorso-median	—	—	Strong	Strong	Strong
—	—	Yes, dorsal	Dorso-lateral	—	—	,,	,,	,,
—	—	Ventral region	Ventral region	(Associations not yet determined)				

In this table it will be noticed that when the roof nucleus alone was injured, or the roof nucleus with the globosus, that the degenerations turned ventrally to come into relation with the nuclei of the oblongata on both sides ; while if the lesion involved the dorsal half of the dentate nucleus or the emboliformis, that the degenerated fibres were only found in the superior cerebellar arm of the same side. The results therefore will be described according as the lesions involved the median group of nuclei or the lateral group.

(*b*) *The Connections of the Medial Group of Cerebellar Nuclei—the Nucleus of the Roof and the Globosus.*

In those experiments on both cats and monkeys in which the roof nucleus was destroyed alone or with the globosus, two distinct tracts of degeneration were observed—the hook bundle, and the fastigio-Deiters, which is included in the juxta-restiform bundle. Both of these tracts connect the medial group of nuclei with the various nuclei in the oblongata. No degenerations have been found in the superior cerebellar arms.

But before proceeding with a description of these results, the work of previous investigators in this field will be briefly reviewed.

The hook bundle ("faisceau en crochet ; faisceau cérébello-bulbaire ; tractus uncinatus ; Hackenbündel ; fibræ cerebello-tegmentales").

The discovery of this tract is generally accredited to Risien Russell [21], who in 1894, after an experimental ablation of one lateral lobe of the cerebellum, found a bundle of degenerated fibres occupying the hook-like extremity of the dorsal region of the opposite superior cerebellar arm, an area which was quite free from degeneration on the side of the lesion. In order to prove that these fibres decussated, Russell divided the cerebellum by a median incision through the vermis and found the degenerated hook bundle occupying the same position in both superior cerebellar arms. He considered the fibres to arise from the lateral lobes of the cerebellum, and traced them to the region of the posterior corpora quadrigemina, where they became intermingled with the fibres of the opposite superior cerebellar arm.

Then Probst [18] in 1902, after removing the lateral lobe of the cerebellum with part of the vermis and injury to the dentate nucleus, mentions among the mass of degenerated fibres the "Hacken-bündel," but in a somewhat indefinite manner. He thought that the fibres probably arose from the roof nucleus, decussated immediately, then ran to the superior cerebellar arm on which they sat like a cap. From here they turned ventrally. But no clear description of their course or termination is given, though he suggests that some of the fibres end in Deiters' nucleus and some run to the sixth nerve nucleus.

Two years later, Lewandowsky [13], following a complete hemisphere lesion of the cerebellum, reported this bundle which he called the tractus uncinatus. He considered that the fibres arose in the roof nucleus, decussated, and then turned ventrolaterally to hook over the superior cerebellar arm. At this point he differentiated three groups :—

(1) The cerebello-tegmental fibres which run along the ventro-lateral surface of the restiform body, to terminate in the fasciculus of Roller and the fasciculus solitarius.

(2) The cerebello-vestibular portion which, after reaching the lateral surface of the restiform body, turns ventrally to descend with its medial fibres. They then turn medially through Deiters' nucleus, without ending there, and finally terminate in the nucleus of Bechterew.

(3) The fasciculus retropeduncularis, which is seen as a round bundle in the dorso-lateral region of the superior cerebellar arm. This passes oralwards and is finally lost in the grey substance of the tegmentum.

In 1906 van Gehuchten [8] reported this bundle as the "faisceau cérébello-bulbaire" or the "faisceau en crochet." He credited the roof nucleus with the origin of the fibres, described their decussation in the white mass of the cerebellum, and their course around the superior

peduncle to curve inward about the restiform body. He considered an anterior and a posterior fascicle—the anterior which descended into the reticular formation of the bulb, and the posterior, which could be followed into the inferior peduncle. He concluded that the fibres terminated in the bulb, without knowing exactly in which grey masses their endings were to be found.

André Thomas [23] reviewed the literature in 1912 and performed some experiments, but contributed nothing of importance. And Marburg [15], in his "Handbuch des Neurologie des Ohres" of 1924, sums up the generally accepted view of this little known tract, by briefly stating that he considered the fibres to arise in the roof nucleus, decussate under the vermis and after hooking over the superior cerebellar arm turn ventrally to end in the vestibular nucleus.

These experiments demonstrate clearly the different opinions that existed in regard to this bundle, and how very incomplete our knowledge of its course was, with no suggestion as to its function. When one considers the gross nature of the lesions which usually involved a quarter or half of the cerebellum, frequently with injury of other nuclei, and the very extensive degenerations that must have resulted, it is not difficult to understand that the course of any particular tract must have been almost impossible to follow.

In the present research, in which I was fortunate to have the very able assistance of Dr. Leo Bartemeier, small lesions, a few millimetres in diameter, were placed directly in the roof nucleus and the globusus without injury to any other structures. From these lesions it has been possible to trace the tracts of degeneration—the hook bundle and the fastigio-Deiters' bundle—from their origin to their various terminations in the medulla, and a very definite idea as to an important part of their function has been determined.

Description of the hook bundle.—Arising from the cells of the roof nucleus and the globusus, the fibres of the hook bundle decussate immediately by several routes. The main bundle leaves the ventral surface of the roof nucleus and crosses at once in the white substance of the vermis, passing ventral to the opposite roof nucleus and dorsal to the lobe of the nodule, over which it swings laterally and ventrally to form a very prominent bundle on the dorso-medial surface of the superior cerebellar arm. The fibres then swing orally to hook over the superior arm, for it is only in sections about 2 millimetres anteriorly that the bundle is found which forms a cap on the dorsal surface of the brachium. From this cap the fibres then turn ventrally, a few passing through the brachium, the majority continuing along the lateral surface of the superior cerebellar arm, then the medial surface of the corpus restiforme

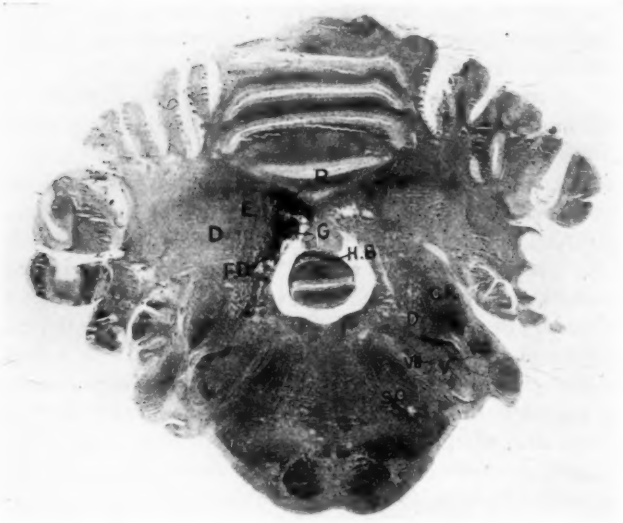

FIG. 6.

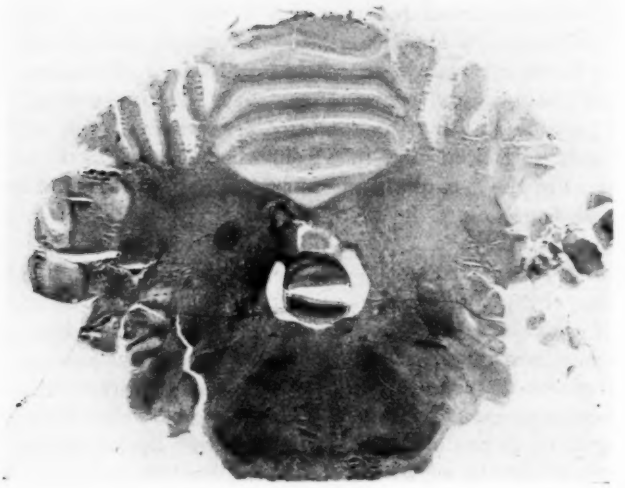

FIG. 7.

FIGS. 6 to 9.—A series illustrating a lesion in the roof nucleus and the globosus, with degeneration of the fastigio-Deiters' tract and the hook bundle. Cerebellar nuclei.—R.G.E.D.; F.D.—Fastigio-Deiters' bundle. H.B.—Hook bundle. N.—Nodule. C.R.—Corpus restiforme. D.—Deiters' nucleus. S.O.—Superior olive. V, VII, VIII.—Cranial nerves. For description of hook bundle and fastigio-Deiters', see text.

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FIG. 8.

FIG. 9.

to the lateral region of Deiters' nucleus, where they become grouped together in a very prominent bundle. The majority of the fibres then enter Deiters' nucleus where they obviously terminate.

The remainder of the fibres are split up into three main groups.

(1) A medial bundle which sends a few fibres to Bechterew's nucleus, the dorsal nucleus of Schwalbe, and a considerable number to the sixth nerve nucleus and the posterior longitudinal fasciculus.

(2) A very compact bundle which passes ventrolaterally between the eighth nerve and the spinal root of the fifth, on the lateral surface of which it divides into two distinct branches—the lateral continuing with the fibres of the eighth nerve to an unknown destination, the nerve having been cut in removing the brain.

(3) The medial branch swings around the spinal root of the fifth, to which it probably sends collaterals, then passes on to the seventh and the region of the tecto-spinal tract. A questionable degeneration was observed in the cortico-spinal tract and around the superior olive. These relations will have to be further investigated.

A second and very important group of fibres passes from the injured roof nucleus directly into the opposite roof nucleus, through which it runs, most probably giving off collaterals. Most of these fibres then join the previous group, but a few continue laterally well above the superior arm and make a definite loop into the ventral region of the dentate nucleus. These fibres then pass ventrally to join the first group; none of them enter the superior cerebellar arm.

A small but interesting third group turns ventrally from the injured nucleus, and swinging partly through and partly around the nodule, joins the first group.

The fastigio-Deiters' bundle.—This tract also takes origin in the roof nucleus and the globosus. Its course is in the mesial arm of the same side in the wall of the fourth ventricle, where it forms part of the juxta-restiform bundle, to Deiters' nucleus of the same side, in which it principally terminates. Some fibres continue to Bechterew's nucleus and some pass mesially to the nucleus of the sixth and the posterior longitudinal fasciculus.

In summing up the connections of the median group of cerebellar nuclei—viz., the roof nucleus and the globosus—it may be said that we have :—

(1) The hook bundle proper, which is a crossed association with Deiters' and Bechterew's nuclei ; the nucleus of Schwalbe; the fifth, sixth, seventh nuclei ; the posterior longitudinal bundle; the region of the tecto-spinal tract; and a questionable relation with the superior olive and the cortico-spinal tract.

(2) A crossed relation with the opposite roof nucleus, probably the emboliformis; and some few fibres to the nucleus dentatus.

(3) The fastigio-Deiters' bundle, which is a direct association with the ipsilateral Deiters' nucleus; Bechterew's nucleus; the sixth nucleus, and the posterior longitudinal fasciculus (figs. 10 and 11).

The function of these median nuclei will be considered in the following section.

(c) *The Response of the Posterior Vermis and the Median Group of Cerebellar Nuclei to Stimulation.*

The very evident association of the roof nucleus and the globosus, through the hook bundle, with the opposite sixth nucleus, and the posterior longitudinal fasciculus, suggested the idea of examining the reactions of these nuclei to determine whether movements of the eyes could be obtained.

With the aid of the stereotaxic instrument a bipolar needle, insulated to within 1 mm. of the points, was inserted into the left side of the cortex of the posterior vermis. On stimulation a bilateral deviation of the eyes to the left occurred, with a slight accompanying movement of the head. And when the needle having passed through the cortex entered the left roof nucleus, there was a conjugate movement of the eyes to the right, with an associated turning of the head. Stimulation in the right half of the posterior vermis resulted in a conjugate deviation of the eyes to the right, and when the needle entered the right roof nucleus the head and eyes turned to the left. These results suggested that there must be a decussation of fibres between the cortex of the posterior vermis and the nucleus of the roof and the globosus (fig. 10).

In the hope of explaining this crossed effect on stimulation, a lesion was made in one of the folia on the left side in a position similar to the one that had been excited. When the sections which had been stained by Marchi's method were examined the degeneration was very clearly shown to pass across the mid-line to the right roof nucleus. The explanation of this will be clear if a series of transverse sections through the posterior vermis is examined (fig. 12).

In the cat the dorsal folia of the posterior vermis usually take the form of an "S" laid horizontally. The folia in the upper part of the "S," which occupy the left side of the vermis, are arranged in a triangular group with the apex pointing to the right. The folia forming the lower part of the "S" are situated on the right side of the vermis, where they are grouped in a semicircle with the centre to the left. A horizontal section through the posterior vermis reveals the fact that

from the folia in the upper part of the "S," that is, those which lie on the left side, all the fibres pass through the apex to the right and on to the right roof nucleus; while the semicircular group of the folia on the *right* side of the vermis send their fibres to the *left* roof nucleus.

What happens on stimulation, then is this: when the cortex on the left side of the posterior vermis is excited—the head and eyes turning to the left—the impulse is conveyed to the right roof nucleus. Here it

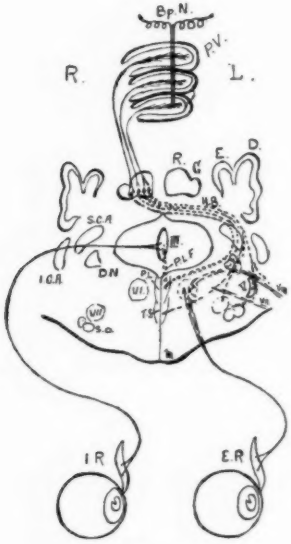

FIG. 10.

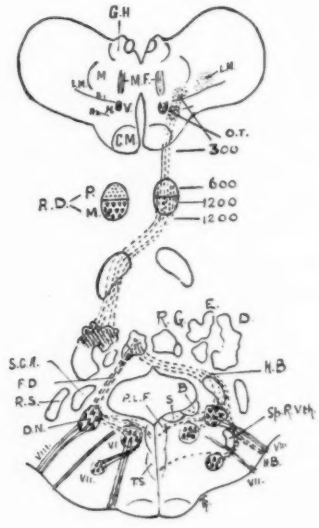

FIG. 11.

FIG. 10.—Bp. N.—Bipolar stimulating needle with 1 mm. of points exposed. P.V.—Posterior vermis. R.—Roof nucleus. G.—Globosus. E.—Emboliformis. D.—Dentate. S.C.A.—Superior cerebellar arm. I.C.A.—Inferior cerebellar arm. D.N.—Deiters' nucleus. III.—Third nucleus and nerve. V.—Motor fifth. VI.—Abducens nucleus. VII.—Seventh nucleus and nerve. VIII.—Eighth nerve. P.L.F.—Posterior longitudinal fasciculus. T.S.—Tecto-spinal tract. I.R.—Internal rectus. E.R.—External rectus. H.B.—Hook bundle. Diagram illustrating the conjugate deviation of the eyes to the same side on which the cortex of the posterior vermis is stimulated.

FIG. 11.—A diagrammatic representation of the degenerations arising from the median cerebellar nuclei—the roof and the globosus, and the lateral group—the emboliformis and the dentate. R.G.E.D.—Cerebellar nuclei. H.B.—The hook bundle. S.C.A.—Superior cerebellar arm. R.S.—Restiform body. D.N.—Deiters' nucleus. VI.—Sixth nucleus and nerve. B.—Bechterew's nucleus. S.—Dorsal nucleus of Schwalbe. P.L.F.—Posterior longitudinal fasciculus. T.S.—Tecto-spinal tract. VIII.—Eighth nerve. Sp.R. Vth.—Spinal roof of fifth. VII.—Seventh nerve. R.P.—Red nucleus. P.N.—Parvocellularis. M.—N. Magnocellularis. G.H.—Ganglion habenulæ. M.F.—Meynert's fasciculus. V.—Vicq d'Azyr's bundle. H.—Field of Forel. C.M.—Corpus mammilare. L.M.—Lemniscus medialis. H.I.—Lamina ventralis and field of Forel. O.T.—Termination of fibres in Forel's field. The numerals 1200, 600, 300, indicate the number of fibres in the different positions. (See text.)

is broken up into its several components, which are necessary to bring about the combined reactions of turning the head and eyes to the left, as well as the necessary co-ordinated response in the general body musculature, for the main characteristic of cerebellar stimulation is a correlated muscular reaction.

The impulses which are responsible for the eye movements are then conveyed from the right roof nucleus through the decussating hook bundle to the nucleus of the left sixth and the external rectus; and by way of the posterior longitudinal fasciculus to the third nucleus and the right internal rectus, thus producing a conjugate deviation of the eyes to the left, that is, the side of the vermis stimulated (fig. 10).

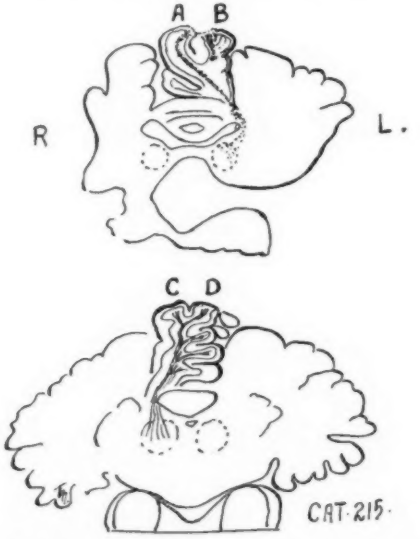

FIG. 12.—Represents horizontal sections through the upper folia of the sigmoid lobe of the vermis of the cat, and demonstrates the decussation of the fibres from the cortex to the opposite roof nucleus. A indicates a folium on the right side of the vermis, the fibres of which cross diagonally to reach the left roof nucleus. B is the upper part of a folium which is continued at D. The lesion involves principally the cortex at B, but some degeneration is also found in A. The degeneration starting at B is continued at D, and can be followed to the right roof nucleus.

When the stimulating needle, having passed through the left side of the cortical folia, enters the left roof nucleus, we naturally obtain opposite reactions, for the impulses will now pass by the left hook bundle to the right side to be distributed to the right external rectus and the left internal rectus, thus producing a conjugate deviation of the eyes to the right.

The accompanying movement of the head is the result of the stimulation passing from the roof nucleus to the ipsilateral Deiters, and by the Deiterso-spinal tract or the posterior longitudinal fasciculus, or the tectospinal tract, to the eleventh nucleus, thus turning the head in the direction of the eyes.

The reaction of the general body musculature will not be discussed at this time.

(*d*) *The Connections of the Lateral Group of Cerebellar Nuclei—the Nucleus Dentatus and Emboliformis.*

On referring to the table of experiments it will be observed that if the lesion of the roof nucleus and the globosus involves even to a slight degree the emboliformis, that a moderate amount of degeneration is found in the superior cerebellar arm, the greater part going to form the

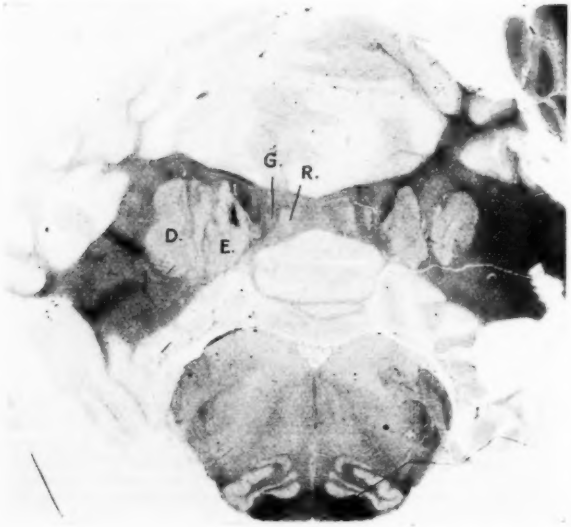

FIG. 13.

hook bundle and the fastigio-Deiters' bundle. But when the lesion involves only the emboliformis and the dentate, then the entire degeneration passes through the superior cerebellar arm of the same side to the opposite red nucleus and the thalamus. I want to mention again that in this series none of the lesions involved the ventral regions of either the dentate or the emboliformis, so that the above remarks refer to the degenerations arising from the dorsal regions only.

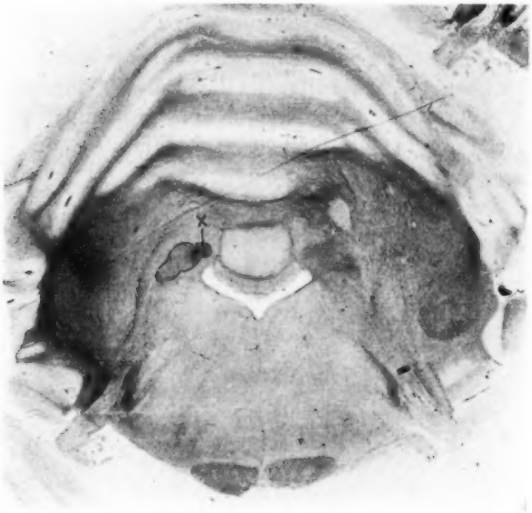

FIG. 14.

FIG. 15.

FIGS. 13 to 15 (*Macacus rhesus*).—This series illustrates a lesion in the dorsal position of the nucleus emboliformis. The degenerated tract occupies a median position in the S.C.A. In the red nucleus, where the majority of fibres terminate, they are scattered. The remainder of the fibres enter the field of Forel. R.G.E.D. represents the nuclei. X indicates the degeneration. F.—the field of Forel. G.H.—Ganglion habenulæ. N.—Meynert's bundle. L.V.—Lamina ventralis. V.d.—Vicq d'Azyr's bundle.

The superior cerebellar arm.—This great efferent tract, the only direct connection between the cerebellar nuclei and the fore-brain, may be described in a general way as composed of fibres which probably take their origin entirely in the nucleus emboliformis and the nucleus

FIG. 16.

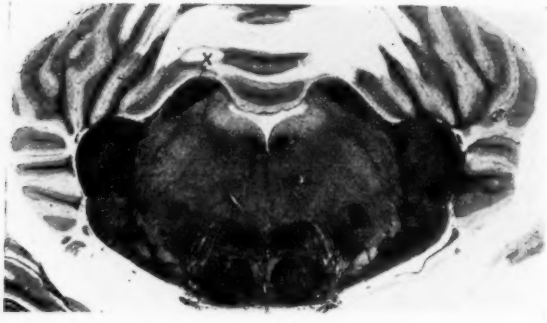

FIG. 17.

dentatus. Grouped together, they form the superior cerebellar arm, which decussates completely, to end in the opposite red nucleus and the thalamus.

But, as will be demonstrated, when experimental lesions involve only

small areas of these nuclei, from which definite bundles of fibres pursue distinct and separate paths, then it becomes necessary to consider, not only each nucleus individually, but the particular region of the nucleus

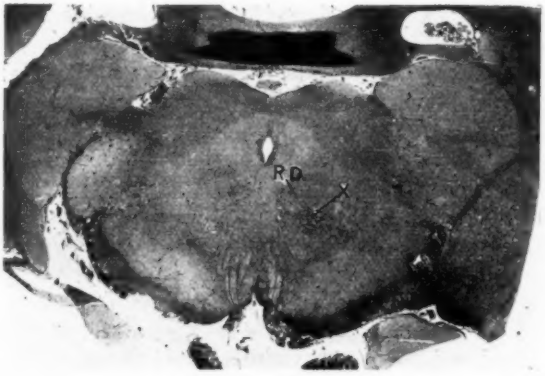

FIG. 18.

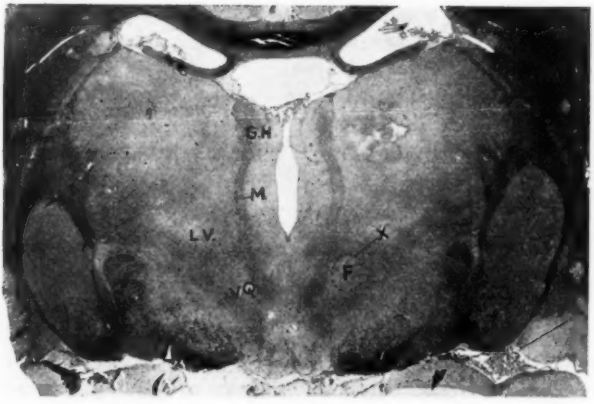

FIG. 19.

FIGS. 16 to 19 (*M. rhesus*).—Lesion of the dentate nucleus. The degeneration forms a compact bundle in the S.C.A. lateral to the fibres from the emboliformis. In the red nucleus they are found grouped about the centre, and in the thalamus they terminate in the field of Forel with the fibres of the emboliformis. D.—Dentate nucleus. E.—Emboliformis. S.C.A.—Cerebellar arm. X,—Degenerated fibres. R.D.—Red nucleus. G.H.—Ganglion habenulæ. M.—Meynert's bundle. V.D.—Vicq d'Azyr's bundle. L.M.—Lamina ventralis.

involved in the lesion. The accompanying illustrations of the degenerations arising from the nucleus emboliformis and nucleus dentatus will illustrate this.

In the nucleus emboliformis the lesion is in the dorsal region of the anterior portion. From this area the degenerated fibres form a compact bundle which occupies the dorso-median extremity of the superior cerebellar arm. The dorsal position of these fibres is maintained in the decussation. But, on reaching the red nucleus, where the majority of the fibres terminate, a general scattering was found both in the nucleus magnocellularis and the nucleus parvocellularis; the comparatively few remaining fibres then passing on to their final distribution in the subthalamic region, where they occupy the field of Forel, ventral to the lamina ventralis and lateral to the bundles of Vicq d'Azyr and Meynert (figs. 13-15).

A lesion was produced in the anterior region of the dentate nucleus. From this area the degenerated fibres again form a well-marked tract which occupies a central position in the superior cerebellar arm. Dorso-medially, as has just been shown, lie the fibres from the oral portion of the emboliformis; the free lateral area probably serving the fibres from the ventral regions of both of these nuclei (figs. 16-19).

The central position of this bundle is maintained in the decussation; and in the red nucleus the fibres are found to be similarly grouped. But the few which proceed to the thalamic region terminate in an almost identical position as the previously mentioned fibres from the nucleus emboliformis; viz., the field of Forel.

In another experiment in which the lesiah was more extensive, the dorsal regions of both nuclei were involved. In this instance the terminations in the fore-brain were divided, the smaller number of fibres entering the field of Forel, while the larger group occupied the postero-median region of the ventral nucleus of the thalamus, just median to the termination of the lemniscus, as observed in several unpublished experiments.

It thus appears that this nucleus of the thalamus acts as a receiving station for the afferent impulses coming directly from the spinal cord through the median fillet, as well as for the correlated impulses from the cerebellum that reach it through the superior cerebellar arm.

In the various experiments on the emboliformis and dentate nuclei no degenerations were observed about the roof nuclei, or in the hook bundle; and the neighbourhood of Deiters' nucleus was quite free.

A question of some interest regarding the degenerated fibres found in the superior cerebellar arm after lesions of the lateral nuclei is, in what proportion do these fibres terminate in the nucleus magnocellularis, the nucleus parvocellularis and the thalamus? To determine this the degenerated fibres in the superior arm both before and after the decussation were counted, they totalled roughly 1,200. In the nucleus magno-

cellullaris the number of fibres was the same. The nucleus parvocellularis contained 600, while those in the thalamus numbered 300. From this it can be argued that all the fibres from the nucleus emboliformis and the nucleus dentatus enter the red nucleus, any fibres that may be given off to the tegmental region being most probably collaterals. So that, speaking in general terms, it may be said that of a given number of fibres entering the superior cerebellar arm of the cat one-half terminate in the nucleus magnocellularis, one-quarter in the nucleus parvocellularis, and one-quarter in the ventral nucleus of the thalamus or the field of Forel. This is also true in *Macacus rhesus*.

(III) The Red Nucleus in the Cerebellar Arc, with a Criticism of the Conclusions of Magnus and De Kleijn as to its Function.

With the object of determining if possible the function and relations of the red nucleus, a number of experimental lesions were made on cats. During three weeks daily observations were taken. The symptoms observed will be briefly described and the results compared with those of Magnus and De Kleijn.

In the first experiment the posterior pole of one red nucleus was destroyed. No rigidity developed, nor was there any disturbance in the "righting reflex."

The next step was to destroy the nucleus magnocellularis on both sides. Subsequent examination showed the destruction of the posterior poles of both red nuclei, with a complete bilateral and symmetrical degeneration of the rubro-spinal tracts. The only symptom was a slight unsteadiness in the gait which lasted two days. During the remaining eighteen days the gait was normal, and the reflexes, sense of position and muscle tone were not affected.

As such an extensive destruction of the nucleus magnocellularis on both sides, with complete degeneration of the rubro-spinal tracts, produced no symptoms, it was decided to try the effect of a lesion on the anterior pole of the red nucleus, the nucleus parvocellularis. In this experiment the lesion was limited to the anterior region of the nucleus on the left side. The nucleus magnocellularis was not disturbed, nor was there any degeneration in the rubro-spinal tract, as it is generally known. But arising from the cells of the nucleus parvocellularis a well-marked tract of degeneration was observed. These fibres crossed immediately and passing under the opposite red nucleus they took up a position in the lateral region of the rubro-spinal tract field; maintaining this relation they were followed to the cervical cord, in the lower segments of which they were lost. This group of fibres might be called the "rubro-

cervical tract," to distinguish it from the rubrospinal which arises from the cells of the nucleus magnocellularis and is distributed throughout the entire length of the cord.

The symptoms observed in this experiment were of great interest :—

First day : The animal was found in a sitting posture, the head, body and tail curved to the right. On moving it turned in a circle to the right, pivoting on its hind-legs. There was loss of sense of position in the left fore-paw. Muscle tone and tendon reflexes were diminished. The "righting reflexes" were completely lost ; the animal could be placed in any position, right side, left side, or on its back, and it would remain as placed without any sign of discomfort.

Second and third day : There was considerable improvement in the muscle tone and the reflexes, and the loss of the righting reflexes was not so marked in reference to the back and left side, but no attempt was made by the animal to right itself when placed on the right side.

Fourth day : There was a decided alteration in the righting reflex. When the animal was laid on the left side it got up at once. If placed on its back it rolled over to the right and stood up. But when placed on the right side it remained lying quietly.

From the fifth day on, the condition generally improved, the disturbance in the righting reflex on the right side gradually disappeared, and through the second and third weeks the only symptoms that remained were some unsteadiness in balancing, and at times a slight turning of the head to the right.

Magnus and De Kleijn [14] in their experimental work on thalamus and decerebrate animals expressed their conclusions as follows :—

(1) If Forel's decussation or the red nuclei are injured, then rigidity always develops and the righting reflexes are lost.

(2) If Forel's decussation or the red nuclei are not injured, then muscle tone remains normal, and the righting reflexes are not affected.

In the second of my series the lesions were shown to involve the posterior regions of both red nuclei as well as Forel's decussation of the rubro-spinal tracts ; that is, a condition somewhat similar to the "decerebrate animal" was produced, and there were no symptoms. According to Magnus and De Kleijn rigidity should have developed and the righting reflexes should have been lost.

In another experiment the lesion involved the anterior pole of one red nucleus, with the field of Forel anteriorly. This produced practically a "thalamus animal" which Magnus and De Kleijn state should show no disturbance in muscle tone or the righting reflexes. But in this specimen there was a marked diminution in muscle tone, and at first complete loss of the body-righting reflexes which later were referred only to the

side opposite to the lesion. In other words, the symptoms produced by minute lesions in intact animals were practically the opposite of those found in thalamus and decerebrate animals.

The point I desire to emphasize is that there is a great difference between the normal animals with otherwise intact central nervous systems used in my experiments, and the thalamus and decerebrate animals of Magnus and De Kleijn. In the first instance, after the minute localized lesions—about 5 mm. in extent—were made, the animals were kept for three weeks, during which time the function of the central nervous system had a chance to recover (with the exception of the parts destroyed); and the structures involved in the lesion were subsequently proved by the degenerations observed in serial sections.

In the experiments of Magnus and De Kleijn we are dealing with animals which possess only the brain-stem. After the operation there is no possibility of a restitution of function, and the animals die within a few hours to a day or so. The object of course was to show by exclusion what parts were essential for the maintenance of muscle tone and the righting reflexes. But even if we allow this argument we cannot overlook the fact that conclusions as to the function of a part, drawn from animals possessing only the brain-stem, should be accepted with great reserve as indicating what the normal function of that part is.

The results obtained by minute lesions in intact animals which retain the possibilities of normal function through the complex association of neurones, should be more reliable and more in accordance with the conditions which particularly concern both the physiologist and the neurologist, than the conclusions drawn from experiments on thalamus and decerebrate animals.

Rubro-spinal tract (*cat*).—So much has already been written about the rubro-spinal tract that it may seem superfluous to attempt another description [16], [9], [5]. But as in no other experiment with which I am familiar have such complete degenerations been found, and as this isolated bundle can be so clearly followed throughout its entire extent in a number of specimens, one more effort to define its course and relations appears justifiable.

The rubro-spinal tract has its origin in the nucleus magnocellularis, which forms the posterior region of the red nucleus. Crossing immediately in Forel's decussation the fibres form an elongated bundle which at first lies dorso-ventrally along the median aspect of the mid-brain ventral to the tectospinal and dorsal to the median lemniscus. In the course of its descent there is a gradual shifting laterally along the surface of the median lemniscus, till it comes to lie in the angle between the median and lateral fillets. At the level of the superior olive the fibres,

which are arranged in quadrangular form, are situated on its dorsal surface. Later, they take the shape of an inverted comma, lying around its lateral surface immediately internal to the seventh root. Opposite the inferior olive they form a triangular bundle in the ventrolateral region of the oblongata; and at the transition of the cord into the medulla, these fibres occupy the angle between the substance of Rolando

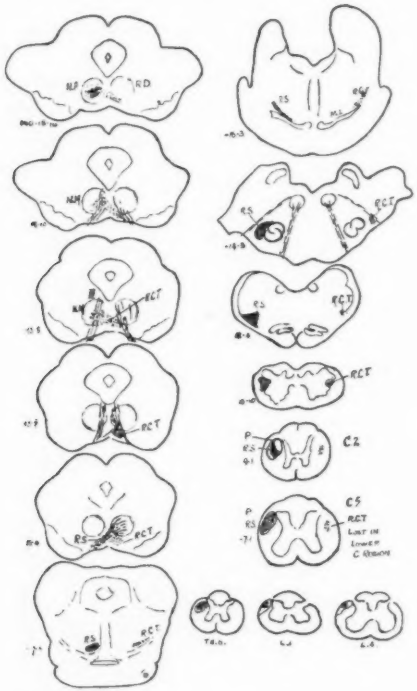

FIG. 20.—Diagram showing origin and distribution of the rubro-spinal and rubro-cervical tracts, also their relative positions in regard to the crossed pyramidal tracts. R.D.—Red nucleus. N.P.—Nucleus parvocellularis. N.M.—Nucleus magnocellularis. R.C.T.—Rubro-cervical tract. R.S.—Rubro-spinal tract. M.L.—Median lemniscus. P.—Outlines of pyramidal tract.

and the anterior horn. In the upper cervical cord their position is within the area occupied by the fibres of the crossed pyramidal tract. In the lower cervical and thoracic segments the fibres are intermingled with those of the crossed pyramidal system; but in the lumbar and sacral regions they are again collected into a rounded bundle which occupies a central position in the crossed pyramidal area (fig. 20).

The rubro-cervical tract (*cat*).—The fibres forming this tract have been so called as they run from the red nucleus to the lower cervical cord only.

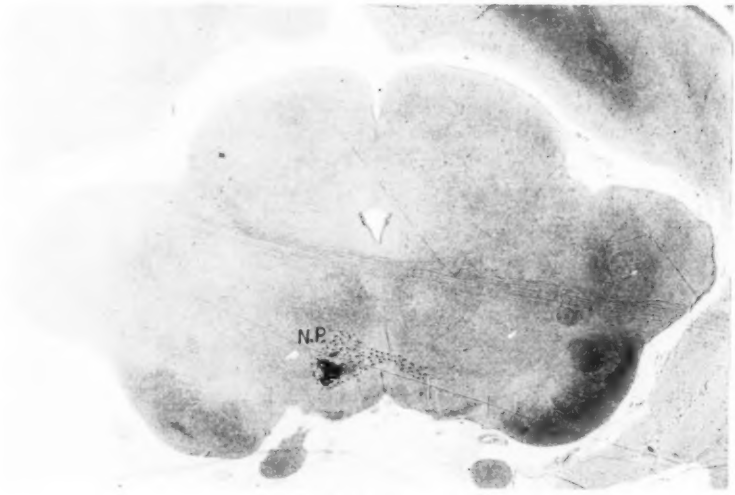

FIG. 21.

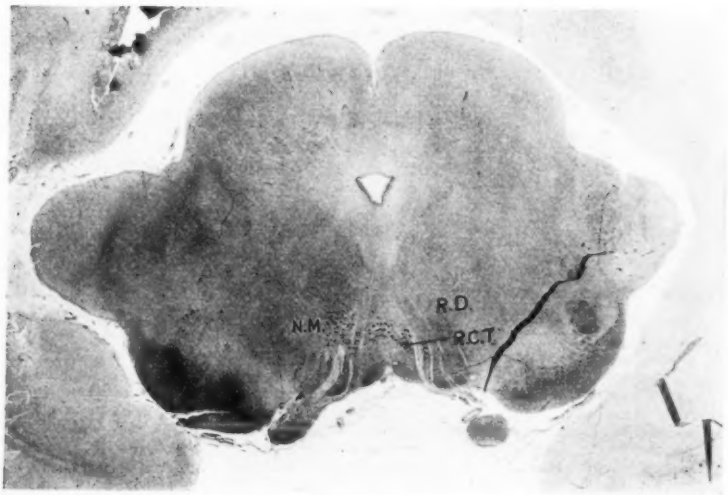

FIG. 22.

Arising from the cells of the nucleus parvocellularis some of the fibres decussate at once, passing into the opposite red nucleus, possibly giving off collaterals ; other fibres run posteriorly into the nucleus magnocellularis and then cross in what is probably the anterior portion of Forel's decussation, and anterior to the decussation of the rubrospinal tract. In a section through the posterior region of the red nucleus these fibres form a loosely arranged bundle immediately ventral to the nucleus magnocellularis, and mostly medial to the fibres of the third root. In the brain-stem the fibres are at first ventral to the rubro-spinal tract, then they gradually assume a lateral position when both these tracts come to lie along the dorsal surface of the median lemniscus. At the

FIG. 23.

FIGS. 21 to 26 (Cat).—A series demonstrating the origin, course and termination of the "rubro-cervical tract."

Fig. 21 shows the lesion in the anterior region of the L. red nucleus, the nucleus parvocellularis being destroyed. The degenerated fibres decussate immediately, as shown in fig. 22. In fig. 23 they are lying along the dorso-lateral surface of the median lemniscus. In fig. 24 they form a perpendicular bundle in the lateral region of the stem. In the next section they are seen as a scattered triangular bundle in the lateral region of the medulla. In fig. 25 they occupy the area between the tubercle of Rolando and the anterior horn. In the upper cervical cord they form a rounded bundle which lies within the rubro-spinal field. Fig. 26 represents the lower cervical region. Here there are fewer fibres, which are much more scattered. No degeneration is found in the upper thoracic segments (compare fig. 26). R.D.—Red nucleus. N.P.—Nucleus parvocellularis. X.—Degeneration. R.C.T.—Rubro-cervical tract. N.M.—Nucleus magnocellularis. L.M.—Median lemniscus. S.C.V.—Ventral spinocerebellar tract. E.R.—Extra-restiform bundle.

level of the superior olive they form a small scattered bundle in the ventrolateral region of the rubro-spinal field close to the seventh root. In the lower region of the oblongata and through the cervical cord they are seen as a diminishing group of fibres occupying the centre of the

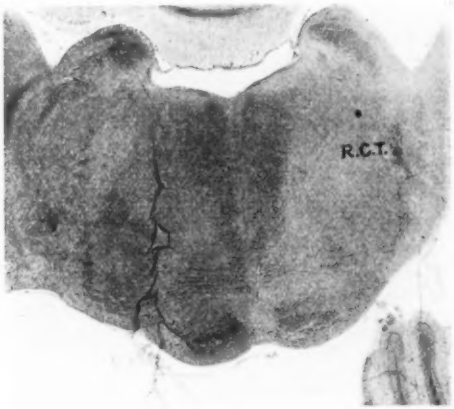

FIG. 24.

FIG. 25.

rubro-spinal tract area, and in the lower cervical region they are entirely lost (figs. 21-26).

As the rubro-spinal tract has been so frequently illustrated, the series of photographs of the unilateral and bilateral lesions of the red nucleus has been omitted. But in the accompanying sketch of a series of

sections from the red nucleus to the sacral cord, the position of the rubro-spinal and the rubro-cervical tracts is shown for comparison, and their relation to the crossed pyramidal system is indicated (fig. 20).

(IV) A Note on the Flocculus.

Bárány's experiments on the flocculus [1] were principally concerned with stimulation. In a number of animals he showed very clearly that the effect of cortical excitation of this portion of the cerebellum resulted in various combinations of eye movements.

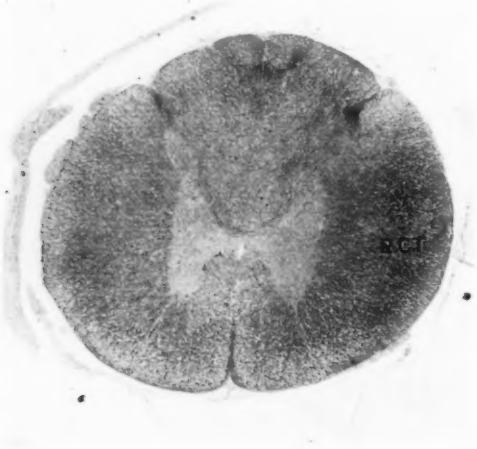

Fig. 26.

In my experiments an attempt was made to destroy the flocculus in the rabbit. Though only a portion of one flocculus was removed, such very definite symptoms resulted, which I believe have not been previously observed, that it seems advisable to report them. On examining the animal a few hours after the operation it was noticed that the "righting reflex" on the side of the lesion was completely lost, and this state persisted with the eyes open or bandaged. A series of very interesting motion pictures shows that the animal quickly rights itself when laid on the sound side, but when placed on the operated side there is no response until the animal is aroused by pinching.

As the preparations of these experiments have not yet been examined, the anatomical description of the lesions will have to be reported later.

(V) Some Preliminary Remarks concerning the Response of the Cerebellar Cortex of the Cat to Stimulation.

(*a*) *The vermis.*—Encouraged by the results obtained on stimulating the cortex of the sigmoid lobe already referred to, an investigation of the reactions in the other lobes of the vermis was undertaken. In these experiments the cortex alone was stimulated, in no instance did the needle enter the nuclei. The general results of these reactions is summarized in the accompanying diagram, representing a medial sagittal section of the vermis (fig. 27).

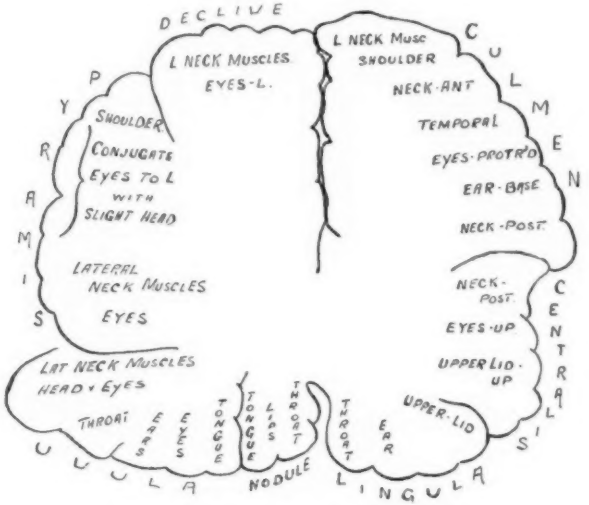

Fig. 27.—Diagram of a sagittal section of the cerebellar vermis of the cat, showing the group reactions obtained on stimulation of the various lobes of the cortex.

On examining these reactions it is interesting to note how muscle responses which are closely associated physiologically are grouped together to form a synergic unit.

In the ventral lobes—the uvula, nodule and ligula—we find the movements concerned in swallowing represented, viz., contraction of the muscles of the throat, movements of the lips and tongue, as well as some associated head and eye movements.

The lobus centralis gives a very interesting correlation of the muscular reactions that are necessary to enable the animal to look upward—eyes turned up, elevation of the upper lids and eyebrows, and contraction of the posterior neck muscles.

The culmen is apparently concerned with the reactions of the muscles on the side of the neck—the anterior and lateral neck muscles, the temporal and ear muscles, as well as various eye movements.

The folia of the declive give reactions in the lateral neck muscles, the shoulder being raised and head bent over sideways. There are also eye movements to the side stimulated.

In the pyramis we have, as previously shown, conjugate movements of the eyes to the side stimulated, with some movements of the head.

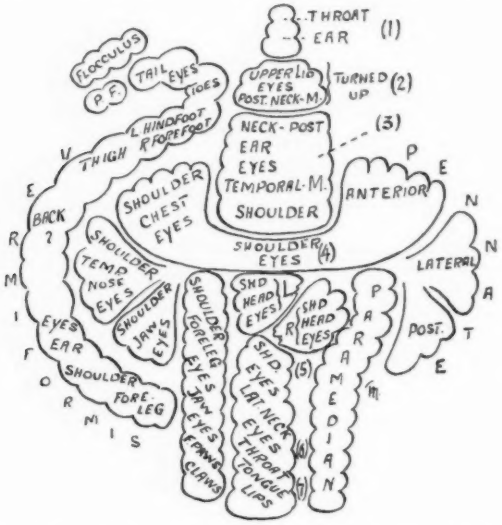

FIG. 28.—The cerebellum of the cat presented on a plane surface. The lobes of the vermis are indicated by the numbers 1 to 7—lingula, centralis, culmen, declive, pyramis, uvula, nodule. The hemispheres are made up of the pennate lobe, the paramedian, and the vermiformis. The most important group responses which were obtained on stimulation of the cortex of the folia comprising these lobes is shown.

(*b*) *The cerebellar hemisphere.*—If the cerebellum of the cat is presented on a plane surface the composition of the various lobes and their relations is quite obvious. In describing these the simplest nomenclature has been used, viz., the pennate, the paramedian and the vermiformis (fig. 28).

The pennate lobe, which consists of anterior, lateral and posterior lobules, forms the bulk of the dorsal surface of the hemisphere. Stimulation of the anterior lobule results in responses of the muscles of the shoulder and chest, with some eye movements. The lateral lobule gives reactions in the shoulder and temporal muscles, while the posterior lobe

is concerned with the shoulder and jaws. Various eye movements were also observed.

The paramedian lobe shows responses in the muscles of the shoulder, upper-leg and fore-leg, with supination of the fore-paw, spreading of the toes, protrusion of the claws, and closure of the jaw. Some associated eye movements have also been noted.

The vermiform lobe, which is very difficult to get at, has not been thoroughly examined. But it may be said from the reactions so far obtained that this lobe is concerned with the movements of the trunk, limbs and tail. The posterior folia give responses in the fore-leg with some eye movements. The folia of the lateral region are probably concerned with the movement of the muscles of the back; while the anterior folia give reactions in the thigh, hind-leg, hind-paw, toes and tail, which was moved to both the right and the left. In all these reactions there are usually some associated eye movements.

These cerebellar cortical responses, which are so briefly reported, have not only been very definitely localized to the side stimulated, but if a similar position in the opposite hemisphere is excited an exactly similar response in that half of the body is obtained. There is little doubt that these reactions are in the main correct, and there is no question of these results being due to the so-called spread of the current.

It must, though, be emphasized that this is but a preliminary report on the reactions obtained in the cat. Many questions naturally arise, and much work has yet to be done. It is my intention to continue with this problem so that it may be possible to present a more detailed account at a future meeting.

These results naturally lead me to the conclusion that the cerebellar cortex is directly responsive to stimulation, and that the character of this response is a correlation of the various muscular reactions which are concerned in some physiological activity, e.g., the conjugate movement of the head and eyes to the right and left on stimulating the posterior vermis, the associated movements which enable the animal to look upwards as found in the lobus centralis, and the movements concerned in swallowing which are represented in the ventral lobes.

It is realized that these conclusions are opposed to those of previous investigators, and that they are based on experiments that are not yet complete; yet as the character of these reactions has throughout been so definite, I feel it advisable to present these views now so that an opportunity will be offered for the consideration of this much discussed and very important question.

The following reactions obtained by stimulating different folia of the cerebellum were demonstrated on a cinematograph.

(1) Posterior vermis, first folium of the left lobus pyramis; movement of the left shoulder.

(2) Posterior vermis, first folium of the right lobus pyramis; movement of the right shoulder.

(3) Posterior vermis, second folium of the left lobus pyramis; movement of the left shoulder, head and eyes to left, twitching of the right ear.

(4) Posterior vermis, left side of uvula: movement of the left shoulder, ears and jaw; vertical movements of the eyes.

(5) Nodulus of the posterior vermis; movements of the jaw, with slight throat and tongue movements.

(6) Anterior vermis, left side of the lobus centralis; movements of the left side of the face, left shoulder and neck.

(7) First folium of the left paramedian lobe; movement of the left shoulder.

(8) First folium of the right paramedian lobe; movement of the right shoulder.

(9) Second folium of the right paramedian lobe; movement of the right shoulder, with extension of the right fore-leg, head to the right and lateral movements of the eyes.

(10) Third folium of the right paramedian lobe; movement of the right shoulder, flexion of the right fore-leg, eyes to left and pupils dilated.

(11) Fourth folium of the left paramedian lobe; movement of the left shoulder, left fore-paw and left eyebrow; rotary movements of the eyes.

(12) Anterior folium of the left lobus vermiformis; movement of the tail to the left.

In conclusion, I wish to thank Dr. Adolf Meyer for his unfailing support and helpful criticism throughout the various investigations.

To Dr. Frederick Tilney and Dr. T. H. Weisenburg I am also deeply indebted, both for their stimulating interest in the work, as well as for the grant from the Association for Research in Nervous and Mental Diseases, without which the research on the cerebellar nuclei had been impossible.

Dr. Leo Bartemeier's very able assistance during the early period of the work, and in the presentation of the paper on the " Hook Bundle " at the meeting of the A.N.A. in 1926, is gratefully acknowledged.

And I desire also to express my thanks to Miss C. Bisson for her careful supervision of the laboratory technique, the excellent photographs and the motion pictures.

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(5) ANATOMICAL AND PHYSIOLOGICAL OBSERVATIONS ON LESIONS IN THE CEREBELLAR NUCLEI IN *MACACUS RHESUS*. (PRELIMINARY REPORT.)

BY ERNEST SACHS, M.D.

AND

EDGAR F. FINCHER JR., M.D.

Fellow in Neurological Surgery.

(*St. Louis, Missouri.*)

IN April, 1924, we received a letter from the late Dr. R. H. Clarke, the inventor of the stereotaxic instrument, requesting that I reinvestigate the cerebellar nuclei, using his instrument, as he and Horsley had never completed the work. Last fall was the first time that an opportunity presented itself of taking up this work and, though it is not yet completed, I feel we have gone far enough to justify making a first report here.

We have had twenty-eight *Macacus rhesus* monkeys for this study, but, on account of the great mortality among them, only twelve have shown satisfactory lesions. It will take another year to complete the study of these specimens.

There are certain points about which there is still a good deal of difference of opinion, while others are fairly well settled, and it is particularly about the controversial points that I want to have something to say to-day.

Horsley and Clarke contended that all fibres from the cerebellar cortex went into the pons or medulla. André Thomas held a different view, and believed that fibres ran from the cerebellar cortex into the spinal cord, but via the restiform body. He was uncertain whether any passed through the superior peduncle.

In using this method, it inevitably happens that a certain number of animals will have lesions not exactly at the point where one hopes to make them, and a millimetre or two difference will make a tremendous difference in the anatomical specimen. We have, however, in our series,

[1] The experiments have all been carried out by Dr. Edgar F. Fincher, Jr., Fellow in Neurological Surgery, and the huge task of cutting all these brain serial sections has been done by him and Mrs. J. L. Ford.

several examples of lesions in different parts of the dentate nucleus, in the nucleus emboliformis, in the nucleus fastigii, and a number of lesions in the area between the cerebellar cortex and the dentate nucleus.

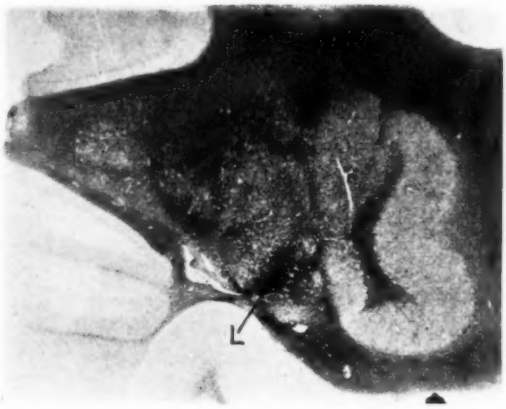


FIG. 1.—Lesion in the nucleus emboliformis, encroaching slightly on the median portion of the dentate nucleus.

FIG. 2.—Fibres are grouped into the hook-bundle, which lies in the median portion of the superior peduncle.

We have one lesion in the cortex of the cerebellum, but as yet have not been able to reconstruct it to know exactly which lobule of the cerebellum the lesion is in.

Comparing the symptoms on stimulation with the anatomical lesions, it seems quite clear that stimulation of the dentate nucleus, as was already pointed out by Horsley and Clarke, produces com-

FIG. 3.—The fibres have left the superior peduncle and are travelling towards the median line.

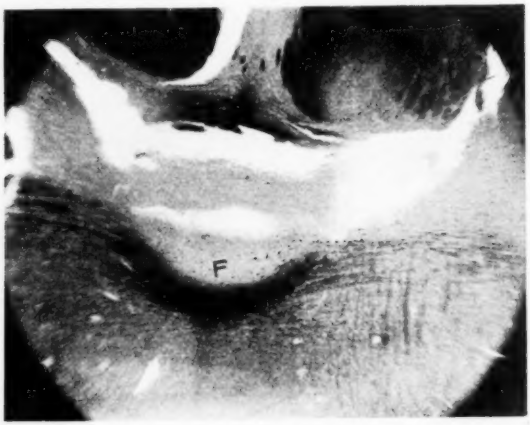
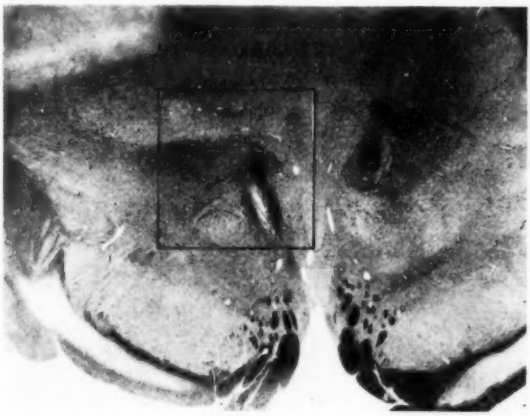


FIG. 4.—The fibres seen in fig. 3 are crossing the median line.

plicated movements, bilateral in character, of the front and hind limbs which they called "progression movements." Our experiments have confirmed this. In addition, however, we have noticed that no nystag-

moid movements occurred when the dentate nucleus was stimulated, though the eyes would be turned to the side of the lesion. On the other hand, with lesions in the nucleus fastigii and nucleus globosus, in other words the median nuclei of the cerebellum, eye movements, both nystagmus and pupillary changes, were the outstanding phenomena. This bears out what we have maintained for a good many years clinically in cerebellar tumour cases, that ocular disturbances, such as nystagmus, only occur if the central nuclei of the cerebellum are involved or pressed upon.



BIOLOGICAL LABORATORY WOODS HOLE

FIG. 5.—Shows the area in which the fibres end, the red nucleus and nucleus of the 3rd nerve.

Tracing the degenerations in these various types of lesions, we have briefly found the following :—

With a lesion of the emboliform nucleus, some fibres run into the median portion of the dentate nucleus, but the bulk of the fibres gather together into a compact group and run forward into the superior peduncle. They are concentrated in the median portion of the superior peduncle (hook bundle). From there they cross the median line through the brachium conjunctivum, and are readily traced to the red nucleus and the region of the third nucleus (figs. 1-5). In a number of cases we have seen what appear to be degenerated fibres in the third nerve. Allen, of the University of Oregon, made a similar observation, but we have come to the conclusion that these are artefacts. Unfortunately, however, Allen published no photomicrographs of his lesions or

degenerations, and besides, his method of producing his lesions was rather crude, the work was done on so small an animal as a guinea-pig and it is quite possible that his lesions were larger than he supposed.

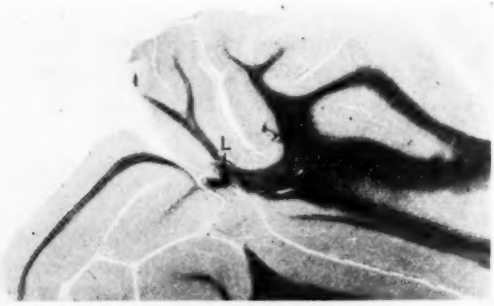


FIG. 6.—Lesion in the cerebellar cortex. No involvement of the cerebellar nuclei.

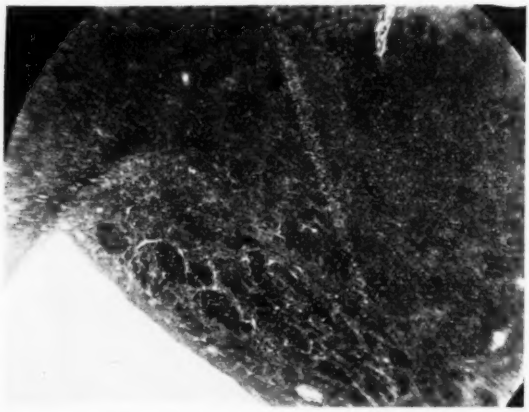


FIG. 7.—The degenerated fibres from lesion in fig. 6 are seen around the diagonal line that runs across the section.

We have studied two cases in which the lesion was in the cortex of the cerebellum, without any injury of the cerebellar nuclei. In both these cases we were able definitely to trace fibres up through the superior peduncle. These fibres cross over through the brachium conjunctivum and some end in the red nucleus and some fibres are definitely traced to the nucleus of the third nerve (figs. 6-9).

FIG. 8.—The fibres from a cortical cerebellar lesion form a compact group in the middle third of the superior peduncle.

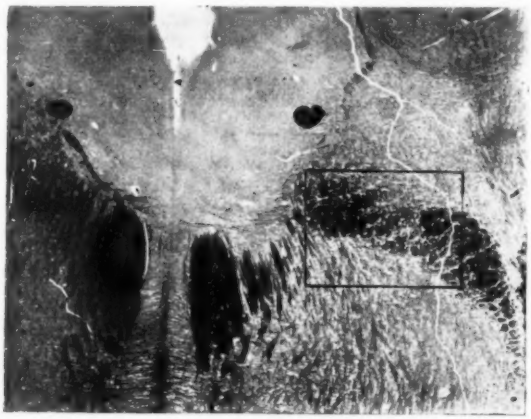


FIG. 9.—Fibres from the superior peduncle turn across the median line just as in fig. 3. These fibres run to the red nucleus and the nucleus of the 3rd nerve.

Conclusions.

The positive findings that we thus far feel we can report are that nystagmoid movements arise from stimulation of the nucleus globosus and nucleus fastigii, while the dentate and the embolus give rise to movements of the fore and hind limbs, but no nystagmoid movements; the only movements of the eyes are those of conjugate deviation which are associated with the turning of the head.

Secondly, that fibres from some of the more laterally placed nuclei in the cerebellum go forward as far as the red nucleus and send fibres into the third nucleus.

Thirdly, that there are definitely fibres going from the cerebellar cortex up into the region of the red nucleus and basal ganglia. Our sections, we believe, show beyond all question that the original contention of Horsley and Clarke, that all cortical cerebellar fibres only go to the nuclei, is not correct.

(6) CEREBELLAR LOCALIZATION AND ITS SYMPTOMATOLOGY.

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INTRODUCTION.

PERHAPS there is no subject in neurology to-day about which there is more controversy than the function of the cerebellum. To a less extent this also applies to the interpretation of symptoms arising from lesions of this organ. In the last decade many excellent papers have appeared on the various aspects of this subject, and while they have enriched our knowledge, they have by no means clarified the problem.

What is the reason for this? The fault in part lies in the nomenclature used in describing the motor disturbances present in cerebellar disease. Some of these are atonia, hypotonia, ataxia, inco-ordination, dysequilibrium, discontinuity, asthenia, astasia, dysmetria, hypermetria, asynergia, anisosthenia, adynamia, and others which have not been mentioned. It is rarely that two authors employ any of these terms in the same way, or attach to them the same meaning. For example, in a recent article, in the description given of the finger-to-nose test, the

statement read that the patient's movements were asynergic, dysynergic, hypermetric and ataxic. Atonia and hypotonia are used to describe different symptoms, but usually the same thing is meant. At times terms are so jumbled up that the reader hardly knows what the author means to imply, leaving him with the well-grounded suspicion that possibly the writer of the article does not himself know.

Perhaps the chief reason for the discrepancies in description is the the fact that *cerebellar disturbances are in motion.* The reeling gait or the inco-ordinate movement of a leg or arm, because of their very nature, are not easy to describe and analyse. Because of this, over twenty years ago, I began to study cerebellar movements by means of moving pictures This was further elaborated by Tilney and Goodhart [1] in the use of slow-moving pictures. Obviously such a study has great advantages, for the camera is quicker than the eye, and what is merely a general impression, as most clinical observations are, is capable of careful analysis.

The assumption that the results of experimental lesions in lower animals are always in accord with human symptomatology, has contributed to the confusion of the subject, for there is no more accord in the experimental results than in the clinical symptomatology.

The purpose of this paper is to discuss mainly two phases of the problem: (1) Localization of function; and (2) symptomatology depending upon such localization. It is my contention that such localization exists, and if this were generally accepted the clinical recognition of cerebellar lesions would be made easier.

The Function of the Cerebellum.

Phylogeny, comparative anatomy, structural connections and histology all point to the fact that the cerebellum is a distinctive organ with a uniform structure with a very definite purpose, and that this purpose is to co-ordinate or synergize all muscular movements. While this is generally admitted there has developed a fundamental difference in its interpretation: (1) Those who believe that the entire organ acts in unison or as a whole; and (2) those who believe that the cerebellum has a functional localization. There are authors who attempt to take a middle ground, admitting that there may be a prevalence of representation of muscle territories in certain large anatomical divisions of the cerebellar lobes. The first viewpoint is largely held by Luciani and Sherrington, who believe that the cerebellum acts as a single function unit, admitting, however, functional supervision over the body musculature on each side of the cerebellum.

It is because of this difference of opinion that much of the difficulty has arisen in the interpretation of cerebellar symptomatology. I believe that there is a very definite localization of function in the cerebellum. If there is not, then the cerebellum differs from every other part of the nervous system. Perhaps much of the confusion has arisen in what is meant by centres. The cerebellum does not act alone any more than any other part of the brain acts alone. The cerebellum exerts its influence at the same time and in conjunction with the other motor levels, in the motor cortex and the corpus striatum—through the lowest motor level in the spinal cord. Whenever the cerebellum is thrown out of function, whatever activity remains is owing to the unopposed action of the remaining physiological levels.

It is not within the scope of this paper to present in full the many evidences which support cerebellar localization. The admitted theories will be briefly mentioned and disputed, or new viewpoints elaborated.

The Phylogeny and Comparative Anatomy.

It is only necessary to mention that from the phylogenetic viewpoint the cerebellum develops according to the needs of the animal for co-ordinate function. The comparative anatomical viewpoint is well summed up by Herrick [2] as follows : The afferent system of fibres is distributed within the cerebellar cortex in an arrangement roughly concentric, and the cerebellar cortex accordingly shows an ill-defined functional localization determined by the distribution within it, ill-defined because there is considerable overlap of the cortical fields reached by the fibre system. He, however, states that the afferent fibres terminate according to their development, the vestibular fibres going to the marginal parts, the mesencephalic and spinal systems more dorsally, and the neopallial system reaching the upper surface farther dorsal than the last. He concludes that on the efferent side of the cerebellum of mammals there is an obscure functional localization, which, like the afferent, may be defined in terms of the anatomical connections of the related fibre tracts.

The Fibre Connections of the Cerebellum.

When considering the question of localization of function in the cerebellar cortex the fibre connections of the cerebellum must be taken into consideration for their course, connections and terminations point to certain physiological conclusions. Our knowledge of these tracts is being constantly enriched by comparative anatomical studies and by such experimental work as is reported in this meeting by Mussen, Sachs and others, and it is altogether probable that in the course of the next few years many contributions will be added which will show that the

cerebellum has many afferent and efferent connections with the spinal cord, medulla, mid-brain and cerebrum which so far have not been demonstrated.

It is held by some authors (Tilney and Riley) [3] that the cerebellar cortex receives fibres from all parts of the cerebral cortex,[1] pons, medulla and spinal cord. These fibres have very definite terminations in the cerebellar cortex. They do not end anywhere. Roughly speaking, most of the fibres transmitted by the inferior cerebellar peduncle go to the vermis, although most of the olivary fibres go to the hemispheres, while those coming from the cerebrum through the middle cerebellar peduncles go to the lateral hemispheres. Through these connections the cerebellum is in contact with all types of receptors; by means of the middle cerebellar peduncles with motor and vestibular impulses from the frontal and temporal lobes, and possibly sensory and visual impulses from the parietal and occipital lobes; by the inferior peduncle with vestibular impulses relayed from the semicircular canals, muscle, joint and tendon sensation by means of the ventral and dorsal spinal cerebellar tracts, these impulses being already co-ordinated and of cerebellar character, and sensory impulses mediating chiefly muscle sense and probably touch sensation by the fibres which come from nucleus cuneatus and gracilis. The function of the olivary cerebellar fibres is not definitely known. They may relay sensory impulses.

There is an extensive bulbo-cerebellar connection between the olivary bodies, the various lateral tract and arciform nuclei, the ocular nuclei, and the fifth, seventh, ninth and tenth cranial nerve nuclei.[2] Exact knowledge of these tracts and of their function is still lacking, but the evidence points that these fibres transmit impulses which inform the cerebellum of the condition of the synergic muscles concerned with talking, eating, swallowing, and movements of the head and eyes.

We have no definite knowledge of the method of termination of the afferent fibres in the cerebellar cortex. The impulses, however, are integrated by the various cortical cells in a manner which has not been determined, and are then transmitted into the nucleus dentatus, emboliformis, globosus and fastigii. There is a very definite order of termination; they do not end blindly, as indicated by Brun [5]. The fibres from the lateral hemispheres or the neocerebellum go into the dentate

[1] There is some doubt that fibres from the parietal and occipital lobes connect with the cerebellum. André Thomas [4] states that the only cerebral connections are with the Rolandic area, the frontal lobe in its orbital portions, and the middle part of the second and third temporal convolutions.

[2] The reader is referred to the excellent paper by Brun [5], which gives a summary of our present knowledge regarding the fibre connections of the cerebellum.

nuclei almost altogether. The fibres from the paleocerebellum, or the vermis and flocculi, go into the nucleus fastigii, globosus, emboliformis, and partly into the dorsal-frontal part of the nucleus dentatus. Here the efferent impulses are again integrated and transmitted to the other parts of the nervous system. Most of these go by means of the superior cerebellar peduncle to the nucleus ruber, and from there to the spinal cord by means of the rubro-spinal tract. These impulses come largely from the nucleus dentatus, but fibres have also been traced from the nucleus globosus, emboliformis and fastigii. The superior cerebellar peduncle also transmits fibres which connect the cerebellum with the opposite cerebrum. These fibres have been traced as far as the optic thalamus.

Efferent impulses are also transmitted into the medulla. They come largely from the paleocerebellum. According to the experiments of Mussen [6], whenever the nucleus fastigii and globosus were injured it was possible to trace two distinct tracts, the hook-bundle and the fastigio-Deiters', into the medulla. The hook-bundle, after decussating, hooks over the superior cerebellar arm and turns ventrally, dividing into a median and ventro-lateral portion. The median fibres pass to Deiters' and Bechterew's nuclei, nucleus triangularis, to the sixth nucleus, and the posterior longitudinal bundle and the tecto-spinal tract. The ventro-lateral portion sends fibres to the motor fifth and seventh nuclei, and some degeneration was traced to the cortico-spinal tract. The fastigio-Deiters' terminates chiefly in the Deiters' nucleus of the same side. Cerebello-bulbar fibres have also been observed as ending in the formatio reticularis of the medulla, where they come in contact with the cells of the dorsal motor nuclei in the medulla. It is reasonable to conclude that through these connections the cerebellum controls the synergic movements of the eyes, talking, eating, swallowing and other bilaterally acting movements.

New rubro-spinal connections are described by Mussen [6]. He destroyed first one posterior pole of one red nucleus, and then of both. When this was done there was complete bilateral symmetrical degeneration of the rubro-spinal tracts, but when he destroyed the anterior pole, i.e., the nucleus parvocellularis of the red nucleus, he found a new tract which crossed immediately and ran laterally to the rubro-spinal field, ending in the lower segments of the cervical cord. He called this the rubro-cervical tract as distinguished from the rubro-spinal.

Before making any deductions as to the physiological significance of such connections, it is interesting to point out that the inhibitory influences coming from the corpus striatum are transmitted to the spinal cord by means of the rubro-spinal tract. What significance does this

have? Does it imply that the function of the corpus striatum and the cerebellum are similar?

While our knowledge of the functions of the red nuclei and rubrospinal tracts has been increased by the experimental work of Magnus and de Kleijn, [7] Rademaker and others, their results have by no means been conclusive. Magnus and de Kleijn in their experimental work on thalamic and decerebrate animals expressed their conclusions as follows: (1) If Forel's decussation or the red nuclei are injured, then rigidity always develops and the righting reflexes are lost; (2) if Forel's decussation or the red nuclei are not injured then muscle tone remains normal and the righting reflexes are not affected.

Mussen [6] came to exactly opposite conclusions as the result of lesions which were shown to involve the posterior regions of both red nuclei as well as Forel's decussation of the rubro-spinal tracts. In another of Mussen's experiments the lesion involved the anterior pole of one red nucleus and probably the field of Forel anteriorly. This produced practically a thalamus animal which Magnus and de Kleijn [7] state should show no disturbance in muscle tone or in righting reflexes, but in this specimen there was marked diminution of muscle tone, and at first complete loss of the body-righting reflexes, which later were referred only to the side opposite the lesion.

Mussen [6] emphasizes the great difference in experimental results obtained in decerebrate animals from those obtained in normal animals, i.e., with intact central nervous systems, for in Mussen's experiments the animals were kept alive for three weeks, during which time the functions of the central nervous systems had a chance to recover.

It would contribute to our knowledge if we knew more accurately the phylogeny, comparative anatomy and tract connections of the cerebral cortex, corpus striatum, red nucleus and cerebellum. It is well known that the corpus striatum, red nucleus and cerebellum have an old as well as a new development, but exact knowledge is lacking as to the relative appearance of these older portions. It is probable that the paleocerebellum develops before the paleostriatum, and that the neostriatum develops before the newer portion of the ruber and neocerebellum. According to Kappers [8] a later development consists in the simultaneous appearance of the cerebral hemispheres, the newer portion of the nucleus ruber or the parvocellularis, in conjunction with the expansion of the lateral lobes of the cerebellum.

These factors argue for a successive development according to the needs of the animal for finer differentiation of movement. It would seem that the older connections subserve a coarser type of movement. This has already been pointed out by J. R. Hunt [9].

Whatever significance the above facts may have, it is obvious that the efferent connections of the cerebellum point to certain physiological conclusions. They are, that by means of the efferent fibres coming from the cerebellum and transmitted by the rubro-spinal and rubro-cervical tracts (Mussen [6]), there is synergic control over the trunk, head and neck, upper and lower limbs, the probabilities being that Mussen's rubro-cervical tract is largely concerned with the head and neck and to a less extent with the upper trunk and upper limbs, and that the cerebello-bulbar tracts control synergic movements of the eyes and also of talking, swallowing, chewing and eating.

To summarize, therefore, the evidence so far advanced, chiefly from the standpoint of the fibre tracts and their connections, it is obvious both from the afferent as well as the efferent side that there is a very definite order in their arrangement for the purpose of first informing the cerebellum of the state of the entire musculature of the body and of the activity of the associating nervous organisms, and after these impulses are received and integrated, wherever synergic effort is necessary, the proper impulses are transmitted through the efferent tracts.

The first attempt at cerebellar localization was made by Bolk [10]. His method consisted in a study of the cerebellum in a large comparative series; he concluded that several parts recognizable in the mammalian cerebellum had definite functional significance and presented areas of central control over definite motor performances in the body. This work was followed by that of van Rijnberk [11], who explored the cerebellar cortex by means of circumscribed extirpations of certain of the lobules. The result of his work confirmed Bolk's hypothesis. These observations have been confirmed in all their essential details by many investigators.

The experimental evidence from stimulation of the cerebellar cortex has been contradictory. Inasmuch as this subject will be discussed in a separate paper in this symposium no extensive reference will be made, with the exception that it is generally held that the cerebellar cortex is inexcitable for movement, and that the central nuclei are. This subject, however, has by no means been settled. In some investigations by Mussen [6], in which he used the stereotaxic instrument of Horsley and Clarke, he was able to get different responses according to the part of the cerebellar cortex stimulated. I witnessed one of his experiments. He has come to the tentative conclusion that each lobe of the cerebellum represents a group reaction, and that the muscular correlation of this group reaction is effected by the combined activity of the folia comprising the lobe. In the lobus centralis, for example, combined muscular reactions are found which enable the animal to look upwards,

i.e., there is contraction of the posterior neck muscles, elevation of the upper lids and upward movement of the eyes; the nodulus gives the reactions of lips, tongue and throat. While these results are tentative, and Mussen has by no means come to a definite conclusion, nevertheless they are suggestive and are in line with the theory held by me.

Clinical Evidence.

There is abundant clinical evidence that there is cerebellar localization. Before presenting my own, I wish to refer to the work of Holmes [12], who studied forty patients in whom there were gunshot wounds of the cerebellum. Of this number twenty-one remained under observation a sufficient length of time to permit of repeated examination and investigation. Holmes came to the conclusion that his observations were only of negative value and that positive deductions could be drawn only from cases controlled by complete anatomical examination, and yet the evidence he presents points to localization. He concluded that the effects of dentate nuclear and cortical lesions differ in no essential particular, but in the latter the symptoms are less intense, less regular, and recover more rapidly. On the other hand, he admits that unilateral lesions produce symptoms which are always limited to the same side. When the vermis was injured the muscles of the head, neck and trunk, including those concerned in phonation and articulation, were more seriously affected, and the disturbance of the function was usually more obvious in mesial than in lesions of one lateral lobe. In comparing the symptoms of unilateral with those of bilateral lesions, the limbs of both sides were affected in the unilateral, but in the bilateral lesions speech was very much disturbed; the muscles of the trunk and neck were very hypotonic and there was difficulty in holding the head in any attitude if unsupported and on sitting up if unaided.

Throughout this excellent paper he points out differences in symptomatology according to the localization of the lesion. On the other hand, Holmes [12] found that cerebellar symptoms were never limited to a segment of a limb or even to one limb. Nearly always both limbs on the same side and the trunk were equally involved. It must, of course, be remembered that the lesions in his cases were the result of gunshot wounds and therefore necessarily somewhat diffuse.

There are, of course, many cases reported in the literature of limited lesions, resulting either from tumour or abscesses, in which the symptomatology has been correspondingly limited. Most of these have been poorly studied, although there are excellent exceptions to this rule. It is a curious thing that in the cerebellar literature there never has been, and there is not now, a consistent attempt on the part of observers to

delimit cerebellar symptoms to parts of the body, most neurologists being content with a proper cerebellar diagnosis. It is this lack of effort or failure to attempt regional diagnosis which has retarded our knowledge and progress in cerebellar localization.

In 1914, Mills [13] and I advanced certain views on the functional localization of the cerebellum. In brief, we placed the function of co-ordination of the limbs in the lateral lobes, for the upper limbs in the superior surface, for the lower limbs in the inferior surface; the centres for movement of bilaterally active functions in the vermis, for the head and eyes, tongue, larynx, pharynx in the upper superior surface of the vermis, and the trunkal movements in the remaining part both superiorly and inferiorly. This localization was tentative and was not intended to be conclusive, but it has served as a working scheme and an incentive to demonstrate cerebellar disturbances in parts of the body. What has been our experience since?

The material which I have has been collected over many years. It consists of moving-picture records of over fifty cerebellar cases. In many the diagnosis was confirmed either by operation or by necropsy. (This paper will be followed by a presentation of the pathological material upon which this study is based.) Some of the moving-picture records were shown at the International Medical Congress held in London in 1913.

When studying a suspected cerebellar lesion I approach the problem from two viewpoints: (1) The proper cerebellar diagnosis, and (2) localization of the lesion. I confess that it is not always easy to make a correct diagnosis of cerebellar lesions, and yet my mistakes have nearly always occurred when the cerebellar symptoms have been unmistakable, i.e., when the asynergia has involved the entire musculature. In such instances tumours of the third ventricle or pituitary lesions have caused secondary dilatation of all of the ventricles, particularly the fourth.

There have been fewer errors in diagnosis whenever the asynergia has been limited to the limbs of one side, or to the trunk either alone or in combination with one of the limbs.

From the standpoint of regional diagnosis, tumour of the cerebello-pontile angle, or of the pons, offers comparatively little difficulty.

Limited lesions within the cerebellum offer even less, provided one is on the look-out for asynergia of one or two limbs, or part of the trunk. Such instances are to be found particularly in acute abscesses following middle ear infections. In growing tumours it is sometimes possible to follow successive involvement of the limbs and trunk.

By the kinematograph, even in a cursory observation, the observer is at once struck with the great diversity in the gait, the station and the

movements of the limbs. No two patients have a similar disability. While in most of them there is disturbance in the gait and in the station, yet there are a large number in which the preponderant disturbances are in the legs, and to a less extent in the arms only, usually associated, however, with an accompanying dysynergia, either of the pelvis or of the shoulder.

Another outstanding fact is that in the station or in the gait there is nearly always a preponderant deviation in a given direction. By that I mean, that if a patient has a tendency in his station to fall to the right he will rarely fall in any other direction, or if in the gait there is a tendency to go forward or backward, or forward and to one side, he will nearly always continue to do so. In the movements of the upper or lower limbs, in the finger-to-nose or the heel-to-knee tests, if there is inward deviation of the upper limb or the leg, such deviation continues throughout the test. The same thing is present in the test for adiadokokinesis, i.e., if there is a tendency of the elbow to turn inwards it remains so throughout the test.

The degree and the nature of the disturbances in the gait and station depend altogether upon whether or not the entire trunk is implicated. It is easily possible to distinguish between the inco-ordinate movement of the entire trunk, of the lower part of the pelvic girdle alone, or of the upper part or shoulder-girdle alone.

In most instances wherever there was a disturbance of synergy in a leg or an arm there was some involvement of the pelvic or the shoulder girdle. The legs were always proportionately more involved than the arms. In many instances, however, the arm or leg was implicated alone.

All the above points are cited to indicate the fact that disturbances of synergy may be present in parts of the body, i.e., in all the trunk or parts of it, in the trunk together with the upper or the lower limbs, or in one limb alone. Further, that the outstanding characteristic of such movements is either a tendency of the limb or trunk to deviate in a certain direction or fail to go in another direction. All this indicates localization of function.

Certain clinical deductions can be drawn from the station and particularly the gait. Whenever the trunkal movements are involved it can be taken for granted that there is a lesion in the vermis. If the patient staggers backwards the probabilities are that the anterior or inferior portion of the vermis is implicated, as in tumours of the fourth ventricle. As will be described later, trunkal disturbances which depend upon lesions of the vermis can be differentiated in so far as they may be limited to either the upper or the lower part. If the upper trunk, the

lesion is probably in the superior vermis; if the lower trunk, the inferior vermis. If the patient staggers preponderantly in a lateral direction, to the right, the right side of the vermis is probably diseased; if to the left, the left side of the vermis. I did not find disturbance in trunkal movements in lesions which were strictly limited to the lateral hemispheres.

The peculiarity of the gait and station and the direction of the movement in cerebellar cases is capable of many interpretations. In this connection Bárány's [14] views are of the utmost interest. He believes that there are not only centres for direction of movement in the cortex, but also a further representation of muscles within these centres according to the articulation moved.

It is well known that in lesions of the vestibular apparatus a differentiation can be made between the symptoms resulting from involvement of the horizontal and vertical canals. In disturbances of the vertical canals there is produced vertical nystagmus, past-pointing in the vertical plane and a tendency to fall backwards or forwards, whereas in lesions of the horizontal canal the nystagmus is mainly horizontal with past-pointing of the extremities in the horizontal plane and lateral deviation of the body. Ingvar [15], who has made important contributions to our knowledge of the cerebellum, supports Bárány's viewpoint, and in addition demonstrated the intimate relationship of the vestibular system with the vermis, the latter receiving practically all the fibres of the vestibular system. He believes that the vestibular impulses are transmitted to the vermis in a similar grouping, i.e., in relation to the horizontal and vertical canals, and that the vestibular innervation of the cerebellar cortex must therefore be arranged on the principle of the different planes of space. He states that lesions of the vermis can to a certain extent be considered similar to the vestibular nerve itself, and that in his experimental animals whenever the posterior lobe—particularly the nodulus and uvula—were removed, the animals had a remarkable tendency to fall backwards, but if the anterior lobe or the anterior vermis was ablated the animals showed a tendency to fall forwards.

Ingvar [15] regards the cerebellum as a reflex organ which preserves the static and dynamic equilibrium of the organism, and that this conception better than any other hypothesis explains the anatomical and histological uniformity of the cerebellum in the whole vertebrate series, and is in accordance with the clinical symptoms of cerebellar disease.

This is an interesting conception but it does not stand the test of clinical facts. For example, in discussing how falling backwards is produced he states, "that if destruction of the posterior lobe elicits falling backwards, we must ascribe to the posterior lobe the faculty of

eliciting in some way the necessary muscular synergies that are necessary to bring about the falling backwards." Further, "that the anterior lobe was related mainly to regulating the motor functions necessary to maintain the equilibrium of the body and preventing the body from falling forwards, whereas the posterior lobe played a rôle in maintaining the equilibrium backwards." These are contradictory statements. To the posterior lobe cannot be ascribed the dual duty of maintaining the equilibrium of the body and preventing it from falling backwards, and if diseased, "eliciting in some way the necessary synergies which are necessary to bring about the falling backwards."

It seems to me that this reasoning is faulty, for it ascribes to a part of the cerebellum which has been destroyed a positive function. Further, he assumes that the cerebellum is alone concerned in equilibration, ignoring, first, the fact that the uninjured portions of this organ have their work still to do, and secondly, that in every posture or movement the cerebro-spinal system and the striatal system are equally concerned.

I believe that the cause of the deviation of a trunk or a limb is a destruction of certain synergic units, and that whatever movement occurs is the result of the activity of the cortical and mid-brain levels and the uninjured portion of the cerebellum expressed through the lowest motor level in the spinal cord.

In this connection I wish to call attention to a very interesting observation regarding the cerebellar gait. In a patient who constantly staggered backwards, when asked to run around on his hands and feet like an animal, he did so with ease. When trying the same experiment with other patients who had trunkal disturbances, they were able to walk on their hands and feet according to the degree of the disturbance of the trunk.

The Nature of Cerebellar Symptoms.

My moving-picture observations, originally reported in 1914, with Mills [13] and further elaborated by the studies of Tilney and Goodhart [1], show beyond question that synergizing of muscular units is the fundamental function of the cerebellum, and that in lesions of this organ asynergia is the fundamental symptom of cerebellar disease. By ultra-rapid motion pictures, and by a graphic record, Tilney and Goodhart showed that synergia is dependent upon two factors, (1) the establishment and maintenance of synergic muscular units throughout the body, and (2) the establishment and maintenance of co-ordination between the synergic units in the performance of complex acts. Throughout the entire body the muscles are arranged in unit groups, each unit consisting of agonists and antagonists. These groups do not operate as an-

tagonists, but as synergists. In a synergic unit two factors may be recognized; (1) the dominant element which determines the direction of the movement, and (2) the check element which works constantly with the dominant in order to provide the necessary limitation so that the resultant movement may at no time be excessive but always exactly adapted to the purpose in hand. The larger the movement the greater the number of synergic units employed. In every muscular act there are two phases, the kinetic and the akinetic. The first produces a motion, the second maintains a fixed position under active contractions of the muscles, such as, for example, in reaching for a glass and in holding it.

If there is a lesion in any part of the cerebellar apparatus there is necessarily produced a disturbance or destruction of the association between agonists and antagonists, and the resulting movement must necessarily be inco-ordinate or asynergic.

Here arises a fundamental difference in opinion as to how the inco-ordinate movements are produced. André Thomas [4] advances the theory which he called anisosthenia, in which he claims that in partial lesions of the cerebellum there may be a loss of tone in some muscles with relative hypertonicity in their antagonists, i.e., that there may be hyposthenia in one group and hyperasthenia in another. This same theory, but couched in different language, is held by most writers on the cerebellum, and is used to explain most of the symptoms of deficit, i.e., the station, gait, dysmetria, hypermetria, adiadokokinesis, and so forth.

It is obvious that a destructive lesion cannot produce any positive symptoms. If, for example, there is a lesion of the right lateral lobe there will be produced an asynergia of the homolateral limbs, but this is not because of the activity of the destroyed area, for this has ceased to function, neither can the remaining uninjured portion of the cerebellum compensate for the destroyed part, for it has its own function still to perform.

My own view is in accord with that of Hughlings Jackson [16], that the cerebellum cannot and does not act alone, that it acts always with the other motor levels in the cerebral cortex and in the mid-brain in conjunction with the lowest motor level in the spinal cord; that if any lesion occurs in the cerebellum the negative symptom consists in the inability of the patient to perform muscular movements in a co-ordinate or synergic manner, and that whatever the patient is able to do, in other words, the gait, the station, the particular movements of the arms which are described under various terms, such as hypermetria, dysmetria, and so on, is the result of the activity of the other motor levels, i.e., the cerebral and the mid-brain levels, acting through a common pathway upon the lowest motor level in the spinal cord.

With this assumption it is obvious that whatever manifestations a patient has depend upon the extent and location of the lesion; the larger the lesion the greater the extent of deficit, i.e., the inability to perform an act in a co-ordinate or synergic manner; and the greater the positive symptoms or the effort of the other motor levels to compensate for the loss of cerebellar function. In a small limited lesion, for example, in a lateral lobe, there need be only disturbances limited to an upper or lower limb, whereas if the lesion is in the vermis the disturbances may be in the trunk as well as the upper and lower limbs, again depending upon the extent of the lesion.

There is also a difference in symptomatology according to how the lesion is produced. In acute lesions certain symptoms will be present which are compensated in a gradually developing degenerative process or in a tumour. There is no doubt that in acute lesions, such as described by Holmes [12], and in traumatic surgical lesions, there is very marked atonia and even weakness in movement, but neither of these symptoms are present in more chronic or tumour lesions. This undoubtedly accounts for the discrepancies in the clinical observations, and it is because writers on the subject have failed to take this into consideration that many of the differences in the clinical descriptions have arisen.

Admitting that *atonia* is present in acute lesions, how is it produced? Ingvar [15], in 1918, suggested that all the various cerebellar symptoms were consequent to a disturbance of muscular tone, following his conception that the cerebellum was an organ regulating the static and dynamic equilibrium of the body. Similar views were expressed by Hunt [9], and by Walshe [17], who maintained that neurologists use the term tone, or atonia, incorrectly. Muscle tone, according to him, should be used in the sense in which Sherrington employs it, i.e., the basis of posture and co-ordinated posture adaptation. By atonia he understands a loss of impairment of the tonic posture reactions of the normal musculature. He then concludes: "May we not suggest that the cerebellum is the organ through which the cerebral motor cortex influences posture activities and regulates posture in the interest of co-ordinated purposive movement?" Is not this conception merely another way of stating that the cerebellum is the organ through which the cerebral motor cortex influences synergic movement?

Asthenia or weakness is undoubtedly present in acute lesions. Holmes [12] gives an excellent description of this symptom, and I have seen it in cerebellar injuries following operations. Such asthenia or weakness in one case under my observation lasted for at least two months and gradually disappeared. It is not, however, present in

slowly developing lesions. Various explanations have been offered for this symptom, such as pressure on the motor tracts, co-existing cerebral foci, atonia, and so forth. Holmes considers it a primary and immediate symptom of cerebellar injury and makes the additional observation that it is probably pronounced only when the cerebellar nuclei are involved and that the fatiguability is dependent on this asthenia.

I believe, however, that another explanation can be offered for the presence of both atonia and asthenia, and that is, von Monakow's theory of diaschisis. In common with the other motor levels, any acute lesion always produces two fundamental symptoms: (1) some impairment of movement, and (2) disturbance of tone.

Cobb [18], in a recent review, summarizes his views on tone as follows: That there are four levels of integration: (1) the main tone posture centres in the medulla, closely related to the vestibular apparatus; (2) the red nucleus and its connections in the mid-brain which control tone; (3) a more complicated control in the basal ganglia; (4) the cortical motor centres which control tone only by abolishing it, when they wish to impose special movements in the place of postures, and concludes that "at present the better evidence points to the simpler explanation: that tonus is a beautifully graded series of proprioceptive reflexes, continuously and unconsciously playing its part in our every motor act. By its remarkable specificity it moulds our individual muscles; by its universality it controls our postures." When considering how intimately the cerebellum is bound up with all of these levels, it is conceivable that in acute lesions there is a temporary disturbance of their function, with the production of atonia and of weakness depending upon the extent of the lesion.

The presence of *nystagmus* and of other ocular disturbances in cerebellar lesions has been disputed. Holmes [12], however, believes that it is extremely probable that nystagmus is due to damage of the cerebellum alone. He states that it varies according to the severity of the injury, and that it may be partly dependent upon the localization of the lesion, though he is unable to state definitely that this is so. He concludes that it seems that each half of the cerebellum has an influence not only on conjugate movement of the eyes towards the same side, but also on vertical movements and on further deviation towards the opposite side, and that it is closely allied to the influences which come from the labyrinths.

Holmes [12] describes five cases in which skew-deviation was observed, i.e., the homolateral eye was directed downwards and inwards, while the other looked upwards and outwards. This is only a temporary symptom.

Nystagmus in cerebellar lesions has been described by a number of observers, but it is not a common symptom, at least, in chronic lesions. I have seen a number of lesions involving the cerebellum in which nystagmus was always more marked on deviation of the eyeballs towards the side of the lesion, but localization was difficult. It is a common symptom following cutting surgical operations.

I have seen only one instance of skew-deviation, and it was present only during a so-called tonic spasm, which will be described later.

I do not believe, however, that *astasia* is present in acute lesions. What is commonly described as astasia is the result of a disturbance of synergy.

The symptoms resulting in acute lesions therefore differ from those which are present in chronic lesions in three things—the presence of atonia, asthenia, and to a less extent nystagmus, these symptoms, however, being present only for a time. They gradually disappear, the time depending upon the extent of the lesion. In every other way the symptoms in acute lesions are similar to those present in chronic lesions, keeping in mind always that the extent and location of the lesion control the symptomatology.

It is not the purpose of this paper to discuss extensively all the symptomatology of cerebellar lesions. I wish to comment, however, upon certain aspects which are well brought out by kinematographic studies.[1]

Abnormal position of the head.—In only two instances have I observed any deviation of the head to one side, and they were in cerebellopontile angle tumours with diplopia. Correction of the same with glasses removed this deviation. In every other instance the position of the head was in line with that of the trunk.

Gait.—A cerebellar patient, when asked to walk across the stage, will take advantage of every sense so as to correct his difficulty in walking. The gait is distinctly modified whether the eyes are open or shut, or by sounds. When walking with the eyes open, the deviation will be at once corrected, or with the eyes shut by the sound of the voice. The cerebellar gait is best demonstrated with the eyes blindfolded and without any sound.

When the entire trunk is involved there is the greatest disturbance in the gait and in the station, and frequently such patients are unable to stand up, or, in attempting to walk, will fall in almost any direction. On the other hand, if the pelvic-girdle is involved alone the trunk is

[1] For a full description the reader is referred to the original paper by Mills and Weisenburg, "Cerebellar Symptoms and Cerebellar Localization," *Journal of the American Medical Association*, 1914, **63**, 1813-18.

held rigidly erect and the legs are pushed forward from the pelvis, giving the impression that the trunk goes after the legs. In extreme cases the patient cannot walk even with help, and, when assisted, the trunk is held rigid and the legs are thrown out in almost any direction. In such cases the upper limbs are usually held partly outstretched and semiflexed at the elbows in an attempt to balance. On the other hand, if the shoulder-girdle alone is implicated the patient usually stands very well and walks almost normally—although he has a tendency to spread his legs apart—but in his station he is likely to fall, and, when walking will lurch usually in a certain direction, giving the impression that the trunk leads, and whichever way it goes, the legs follow.

An excellent way to differentiate between pelvic-girdle and shoulder-girdle asynergy is to have the patient get up from a recumbent posture. In his efforts to do so, while his hands and feet are extended, if the pelvic-girdle is involved alone, there is a distinct to-and-fro swaying of this part, the shoulder-girdle remaining stationary. The contrary is present when the shoulder-girdle is involved.

The nature of the movements of the arms and legs.—This varies considerably. There is a slowness in the initiation of the movement, but it is not present in all cases. After the movement starts, it is slower than normal, although in some it is faster, and in nearly all instances there is an overshooting. There is so much variation, however, in the movements of the limbs that my general impression is that the tempo depends upon the extent of the lesion—the larger the lesion the slower the movement and the greater the oscillations and the overshooting. In smaller lesions the movements are more rapid, as if the patient is making a conscious effort to overcome the disability.

In kinematographic studies the nature of such movements is beautifully shown. It does not matter what test is used, the movement is always the same—although it depends upon the acuteness and extent of the lesion. I believe that such symptoms as dyssynergia, hypermetria-dysmetria, adiadokokinesis, the rebound phenomenon, and all other symptoms which are used in the description of cerebellar lesions, depend upon the fundamental symptom, i.e., the degree of asynergia present. If this were recognized and adopted a great service would be rendered to cerebellar symptomatology, and there would be an abandonment of the attempt to explain each one of these symptoms by some special disturbance. For many years, both in teaching and in writing on this subject, I have abandoned this complicated terminology and have described all symptoms of cerebellar deficit, no matter how obtained, under the term of asynergia, describing, however, how obtained and the extent of it.

Tremor is not a distinct symptom of cerebellar deficit. It can be brought out in every patient, but it is due to disturbance of synergy, and depends upon the extent of the lesion.

Catalepsy.—I was unable to demonstrate this in any of my patients. In putting them on their backs, with the arms held upwards and the legs flexed at the knees, it was noticeable that the limbs on the injured side always drooped first, quite the contrary from what is to be expected from Babinski's description.

Fatiguability.—It has seemed to me that in most of the cerebellar cases it is possible to demonstrate a fatiguability in the limbs of the affected side. In placing a patient on his back and asking him to fold his arms and attempt to assume a sitting position, the legs on the involved side always give way perceptably. In fact, this is a constant observation, and I always look for it in cerebellar patients. Persistent efforts, such as walking, holding weights, or moving the arms and legs, always show an early fatiguability, but it is not because there is weakness of the limbs.

Facial and emotional expression.—This is not as a rule disturbed unless there is difficulty in articulation and phonation, when the face seems less mobile and talking more of an effort.

As a rule the emotional expression is not involved, but here again it seemed to me that whenever there was difficulty in talking, the face appeared to have less expression in it, and that it was difficult for the patient to laugh. In one patient, described by Mills, in whom there was a thrombosis of the superior cerebellar artery on one side, with a lesion extending into the dentate nucleus, there was complete loss of emotional expression on one side of the face, although the muscles could be used for every other purpose.

Tonic spasm.—This was seen by me only in one patient. It was in a man of 20, who had a left cerebello-pontile angle tumour about the size of a hen's egg, which grew from the auditory nerve and extended downwards through the foramen magnum along the medulla. The lesion was diagnosed in life and confirmed by necropsy. I saw one seizure, which began by a turning of the head to the right, then a retraction backwards with the vertex pointing to the left. Coincidently the left arm was lifted above the head, the arm flexed at the elbow, wrist and fingers and deviated outward and downward. At the same time the left leg was lifted from the bed and extended straight outwards. The right limbs were not moved, but were rigid. The left leg was in a tonic spasm, and there were no twitchings.

Coincident with the deviation of the head, both eyes jerked to the right. The movements began about the mid-point, the quick compo-

nent being to the right. The nystagmoid jerkings were followed by a skew-deviation, i.e., the right eye was up and out, the left down and in.

During the attack it was possible to obtain a bilateral extension of both toes in plantar stimulation. The patient was stuporous, but was able to execute some commands. His pulse was slow, about 60 to the minute. He was generally pale and respiration was rapid. The right pupil was larger than the left. After the attack it came to normal. The Babinski reflex disappeared on the right side in about ten minutes, on the left it persisted.

The duration of the entire attack was three minutes. The skew-deviation lasted five minutes and disappeared slowly.

The maintenance of the deviation of the head to the right and backwards and the tonic condition of the left limbs lasted about three minutes. It was impossible to turn the head in any direction during the attack. Afterwards deviation of the head did not produce contracture of the limbs.

This very interesting case presented a tonic spasm, in which the position of the head and the limbs on the left side was very similar to the description given by Hughlings Jackson [16], excepting that the fingers were not clenched and that the spasm was unilateral, i.e., involved only the limbs on one side. The simultaneous extension of the left limbs with the deviation of the head and neck to the right is an example of the Magnus and de Kleijn reflex.

The tumour, which was a neuroma growing from the auditory nerve, was quite large and cystic, and did not directly involve the cerebellum. The sensory fifth, sixth, and seventh cranial nerves were involved by pressure. An interesting feature, however, was the fact that the tumour extended into the internal auditory meatus and was very firmly attached. The specimen was studied by Dr. E. A. Case, who reported it as follows: "A part of the petrous portion of the temporal bone was decalcified and the auditory nerve dissected out as far as its division into the cochlear and vestibular branches. The rest of the bone was embedded in celloidin. The preparations were not as satisfactory as one could wish, and it is well to remember that the structures of the internal ear disintegrate rather early unless promptly and thoroughly fixed. The nerve was most certainly involved as far as its cochlear and vestibular branches, as it had the same appearance as the portion found attached to the internal auditory meatus. Beyond this point we could not go. In the sections of bone no normal cochlear tissue was found, and in the spaces taken for this structure there was destruction of the normal architecture. The semicircular canals did not appear to be involved to the same extent.

"While our study was not as satisfactory as it should be, yet I feel

that we are justified in believing that the nerve was involved up to its division into the cochlear and vestibular branches, and that there was an associated degeneration of the structures of the internal ear."

I do not know how to interpret the presence of the tonic spasm and the skew-deviation. In Jackson's case there was a tumour of the middle lobe of the cerebellum. Here the cerebellum implicated was by pressure. The involvement of the vestibular and auditory nerves must, of course, be taken into consideration.

Conclusion.

(1) The function of the cerebellum is to synergize all motor activity. The cerebellum never acts alone. Its activities are correlated with the other motor levels in the cerebral cortex, mid-brain and spinal cord.

(2) Lesions of the cerebellum produce positive and negative symptoms. The positive symptoms consist in an inability to perform synergic movements properly. The negative symptoms, i.e., the difficulty in movements, whether of the trunk or limbs, are the result of the activity of the other motor levels in the cortex and mid-brain acting through the spinal cord.

(3) There is functional localization in the cerebellum. In the vermis are represented the synergic activities of the trunk; in the superior vermis the movements of the shoulder-girdle or the upper trunk; in the inferior vermis the pelvic-girdle or the lower trunk. Synergic activities concerned in talking and movements of the eyes are located in the vermis, in all probability in the superior vermis. Synergic control of the limbs is in the lateral hemispheres, for the upper limbs in the superior portion, for the lower in the inferior.

(4) There are no centres for deviation in the cerebellum.

(5) The fundamental defect symptom of a cerebellar lesion is asynergia. Such symptoms as dysmetria, hypermetria, ataxia, adiadokokinesis, are all the resultants of disturbance of synergy.

(6) The recommendation is made that the complicated terminology used to describe symptoms of cerebellar deficit be abandoned, and that instead actual symptoms be described in terms of loss of synergy.

(7) The extent of the synergic disturbance present depends upon the nature, extent, and localization of the lesion.

(8) In acute lesions atonia and asthenia are present. This probably results from a temporary disturbance of the other motor physiological levels. In all other ways symptoms of acute and chronic lesions are similar.

(9) In every cerebellar patient an attempt should be made to delimit cerebellar symptomatology to parts of the body with a view to localization of function.

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DISCUSSION.

Dr. F. M. R. Walshe dealt with "The Significance of the Voluntary Element in the Genesis of Cerebellar Ataxy."

The wide range covered by the papers which have just been presented to us affords ample evidence of that fascination which the cerebellum has long possessed for anatomist, physiologist and clinician. In respect of the study of cerebellar functions we seem to be at the beginning of a new epoch, and in the experiments recorded by Pollock and Davis we have some of the first fruits of an approach to this difficult problem from a new angle and directly inspired by the teachings of Sherrington and Magnus.

The moment seems apt therefore for a review of the present state of knowledge and for an attempt at formulation of the problems which remain for solution.

It is approximately forty years since Luciani gave us his admirable descriptions of the disorders of muscular movement produced by destructive lesions of the cerebellum in animals. These disorders he grouped under the three headings of atonia, astasia and asthenia. To say that his analysis is not final is in no way to depreciate the work of the great Italian physiologist. In the light of present knowledge of the nervous control of movement, it is clear that the difficulties which confronted him were wholly insurmountable at that time. How was it possible for him to form any final conception of cerebellar functions when the fundamentally important contributions of the cereberal motor cortex, the brain-stem and the spinal cord, to the co-ordination of movement were completely unknown? The cerebellum was but a single one of a series of unknown factors in this field of nervous activity, and the most that could be achieved was to provide an accurate basis of description for future analysis, couched in a precise and simple terminology. Both these things Luciani did for us, and it must be admitted that while we have been able to add little of material value to the former, we have sadly complicated the latter.

In the routine examination of a case of cerebellar disease we have come to employ a conventional series of test movements from which there result particular expressions of inco-ordination of movement. For each of these one or more special terms have been coined, and with a delightful inconsequence each writer has used these classic euphonies in his own private sense, until many of them have lost any precise and generally understood significance they may originally have possessed.

The fruit of this redundant growth of an unscientific terminology is, as Dr. Weisenburg has pointed out, that we have not yet reached agreement as to what are the essential components of the cerebellar symptom-complex, while the problem of cerebellar functions remains where Luciani left it nearly half a century ago.

We have welcome indications to-day, however, that this phase of purely descriptive investigation has ended, and that observers are turning to new and more fruitful sources of inspiration for their labours.

During the past thirty years, in an unbroken and happily still continuing series of researches, Sir Charles Sherrington has given us a precise description and analysis of the reflex functions of the spinal cord and brain-stem. We have learned that within these structures are laid down mechanisms which render possible as reflex reactions those muscular activities, phasic and postural, which underlie all the co-ordinated movements of the intact animal. In virtue of these mechanisms the animal is automatically kept right side up in a world through which he can move in orderly fashion. Recently this work has been amplified

by the beautiful researches of Magnus and his school, who have analysed with remarkable refinement the reactions concerned in the regulation of posture.

Further, tackling the problem from another angle, Sherrington has given us an insight into the manner in which these subordinate motor mechanisms are played upon by the cerebral motor cortex in the production of the voluntary motor activities of the normal animal.

The physiologist has therefore, as it were, led us to the threshold of the cerebellum and has placed at our disposal great and indispensable resources of exact knowledge as to the modes of activity of the nervous system, and also a scientific terminology on which we may fruitfully model our own recorded observations. It is only within the past few years that the clinician has begun to realize the value of these resources, armed with which we are now for the first time in a position to attempt to determine, not only the *extent* of cerebellar participation in the complex nervous processes governing movement and posture, but also its probable *manner* of participation.

We must not overlook, however, that in this essential preliminary delimitation of the scope of cerebellar activity by the process of exclusion, one very important contribution has come from the clinical observer. I refer to the demonstration that, although the cerebellum stands in relation to the non-sensory component of the afferent nervous system, it has nothing to do with the purely sensory component. To the studies of Holmes, more than to any other, we owe this knowledge.

Let us now consider the exact features of the problem which confronts the student of the cerebellar symptom-complex resulting from lesions confined to the cerebellum. In these circumstances it is disorder of *voluntary* movement that is in question. He sees the result of a general reaction of the intact parts of the nervous system after a more or less complete falling out of the cerebellar component. From this complex pattern, an algebraical summation of many activities, he has to infer the normal features of the lost cerebellar component.

The lack of success which has so far attended every effort in this direction makes it quite clear that the problem must be approached in some other way, and the obvious step is to rule out altogether the element of volition and to study the effects of decerebellation in the reflex or decerebrate animal, in circumstances where each of the many known components of co-ordinated movement can be investigated separately. It is to the study of such reflex animal preparations that we owe whatever advance in our knowledge of the cerebellum has been achieved, though it is true that most of these studies have not had as their immediate purpose the elucidation of cerebellar functions.

From the spinal, ponto-spinal, mid-brain and thalamus animals we have learned that practically all the reflex reactions, phasic and postural, essential to normal co-ordinated movement, are functions of the spinal cord and brain-stem, and that the arcs concerned do not traverse or enter the cerebellum. The thalamus animal without a cerebellum possesses intact all its righting, tonic and phasic reflexes, and can both run and jump, alighting nimbly on its feet. We must conclude, therefore, that the cerebellum takes no essential part in complex reflex reactions involving the movements of the animal as a whole or in part. In the strict sense of the terms, therefore, the cerebellum cannot be held responsible for the regulation of tone, posture, or equilibrium. *There is no such phenomenon as cerebellar ataxy in the reflex preparation.*

The interesting experimental observations of Pollock and Davis may appear to call for some modification of this generalization. Thus, they find that extirpation of the cerebellum in the decerebrate animal is followed by an increased intensity of the tonic labyrinthine reflexes acting on the neck, and also a tendency to increased rebound extension in certain spinal reflexes.

Further, they have investigated the question of cerebellar intervention in the production of reciprocal innervation, but here, as was to be anticipated, found no evidence of such intervention. Indeed, reciprocal innervation is at the very foundation of the simple reflex reaction, and it is unthinkable that it should be in the remotest degree dependent upon cerebellar influence.

Therefore the general statement holds good that the sum-total of tonic and phasic reflex reactions underlying co-ordinated movement remains intact in the absence of the cerebellum.

It is solely voluntary movement, therefore, which is dependent upon cerebellar activity.

It is at this point that we may profitably turn again to the study of the decerebellate animal. In a dog deprived of its cerebellum, but with nervous system otherwise intact, Rademaker confirms the persistence of all those reflex reactions we have seen in the thalamus, ponto-spinal and spinal animals. It is clear, therefore, that the view which I expressed some years ago (*Brain*, 1921, **44**, 539) that a simple loss of all postural reactions, that is, a loss of postural tone in the physiological sense, is the basis of cerebellar ataxy must be qualified. To this point we will return later.

Further, anyone who has handled Rademaker's dogs must admit that simple atonia, in the sense of undue flaccidity and extensibility of muscles, is not present in them some months after extirpation of the

cerebellum, at a time when they still present all the features of gross ataxy of movement.

What has clearly emerged from Rademaker's observations is that many motor reflex reactions, both phasic and postural, are increased in intensity by decerebellation and lose some of that refinement of adjustment we have seen them to possess in the thalamus and ponto-spinal animals. In other words, these reactions are not lost, but are "released" from control when the cerebellum is extirpated, but the cerebral cortex remains in action.

In striking contrast to this state of affairs is the almost complete lack of any such indication of release with its resultant ataxy in the exclusively reflex activities of the thalamus and ponto-spinal animals after decerebellation. It appears, therefore, that it is only when the cerebral motor cortex activates the reflex mechanisms of brain-stem and cord that cerebellar intervention in the motor taxis of the organism occurs. It seems to me imperative that this proposition should be borne in mind in any consideration of cerebellar functions, and inevitable that any theory on the subject which is not based upon it should fail to generalize the observed facts. The most recent review of cerebellar physiology is given by Fulton in his book, "Muscular Contraction and the Reflex Control of Movement." Here all the relevant facts of the physiology of brain-stem and cord are marshalled, but the fundamental importance of the voluntary or cortical element in cerebellar ataxy is completely overlooked, and in formulating his conclusions on cerebellar functions Fulton is, in consequence, forced back upon the old vague conceptions as though these facts had no existence.

It seems reasonable to infer, therefore, that the secret of cerebellar functions is to be sought in a close functional relationship between cerebral motor cortex and cerebellum, and not in any direct participation of the cerebellum in those reflex activities of brain-stem and cord which subserve the elements of co-ordination.

In some as yet undetermined way the cerebellum is functionally interposed on the pathway between the cerebral motor cortex and those subordinate motor mechanisms which the researches of Sherrington and Magnus have shown to exist in the brain-stem and spinal cord. In seeking to determine the manner in which the cerebral motor mechanisms employ the cerebellum we may usefully turn to those views of cortical motor action which have been formulated by Sherrington and Leyton. They have pointed out that all the reflex reactions we have been considering are large movements employing one or more limbs as a whole, while the movements obtained on cortical stimulation are fractional parts of these, and they suggest that the essential function of

the excitable motor cortex is the synthesis of an infinite number of purposive movements from the component parts of these larger movement complexes. The motor cortex selects and combines, into an infinite number of combinations and sequences, the component elements of the simpler movements represented in spinal cord and brain-stem, and is therefore both an analytic and a synthetic organ. It is, in Sherrington's words, "an organ for the synthesis of movements—and postures—on a vast scale."

May it not be that the cerebellum finds its essential function somewhere in this process of synthesis and analysis, that it is an executive organ of the cerebral cortex to this end?

Let us now consider the theory of cerebellar function associated with the name of Tilney. According to this, the muscles are functionally arranged in "synergic units," antagonistic pairs. The relation of the two is not, however, one of reciprocal innervation, a mode of innervation which Tilney appears to regard as not obtaining, but one in which both elements are in active contraction simultaneously, though not with equal force. The more powerfully acting agonist determines the direction of movement, and the less active antagonist acts as a check upon its partner: hence the names "dominant" and "check" elements. The adequate co-ordination of activity with the unit is spoken of as "simple synergia," while the harmonious combination of several units in action in large and complex movements is spoken of as "integrative synergia." The essential result of a falling out of cerebellar activity is asynergia, that is, a loss of co-ordination between dominant and check elements within the unit. This loss is determined by a falling off of the activity of the check element, which allows excessive activity of the dominant element and a consequent excessive excursion of the moving part followed by voluntary efforts at correction. This in turn necessarily disturbs integrative synergia and thus arise all the phenomena of cerebellar ataxy.

In its simplicity and lucidity this conception is undoubtedly most attractive, yet it cannot be accepted without essential modification when we come to assess it in the light of the physiological considerations we have already discussed.

With the objection to the law of reciprocal innervation we need not greatly concern ourselves. It arises from a misconception of what is claimed for the law. In his paper on "Reflex Inhibition as a Factor in the Co-ordination of Movements and Postures" (*Quart. Journ. Exper. Physiol*, 1913, **6**, 251), Sherrington pointed out that simple reciprocal innervation does not meet the complex situation arising in voluntary movements, and he showed that a process of "double reciprocal innerva-

tion" is in action in these circumstances, a mode of innervation in which both agonist and antagonist may be actively contracting at the same time according to laws which he was able to elucidate.

The essential difficulty we have in accepting Tilney's hypothesis as it stands is the statement that the relations of agonist and antagonist, Sherrington's first grade of co-ordination, are a function of the cerebellum and are profoundly upset when this organ is out of action. This view cuts across all we know of the facts of reflex action. It is incredible that this high-level, suprasegmental organ should be involved in the elementary processes of simple co-ordination: processes which we know the simple spinal arc to be perfectly able to accomplish. Further, if it were so, then the reflex movements of the decerebellate thalamus and ponto-spinal animals would be as ataxic as the voluntary movements of the decerebellate but otherwise intact animal. This we know not to be the case.

The disorder of voluntary movement we know as cerebellar ataxy must certainly arise at a much higher physiological level than this hypothesis supposes.

On the other hand, a disturbance of integrative synergia, if we understand by that a disturbance of that cortical process of motor synthesis to which we have already referred, may well underlie cerebellar ataxy. To this extent Tilney's hypothesis is in accord with established facts of physiological observation. That is to say, a disorder of the first grade of co-ordination, that which concerns the harmonious relations of agonist and antagonist, cannot be accepted as the basis of cerebellar ataxy, but the disorder of some higher grade of co-ordination involving the participation of the cerebral motor cortex and concerned with the harmonious relationship between component co-ordinated units of large voluntary movement complexes may conceivably be the basis of the cerebellar symptom-complex.

The essentially cerebral origin of the so-called cerebellar ataxy may be emphasized by defining the latter in general terms as that disorder attending voluntary movement when cerebellar activity is impaired or lost.

It is extremely doubtful whether the experimentally and clinically acquired knowledge of the nervous regulation of movement so far available allows of a final estimate of cerebellar functions. Nevertheless, it is interesting to explore the relevant facts of observation still further than we have done for any indications on the matter they may afford.

Rademaker's observations on the decerebellate dog indicate that the motor mechanisms of brain-stem and cord when activated by the cerebral cortex in the absence of the cerebellum show a departure from normal

in two directions. They are increased in intensity and impaired in refined adjustment to purpose. This twofold change is characteristic of all the so-called "release symptoms" which follow lesions at the various physiological levels of the motor nervous system; but the latter element, namely, that of impaired efficiency or degradation, is apt to be overlooked in favour of the element of overactivity. Yet degradation is equally constant and typical. Thus, the tonic neck reflexes and the whole group of "standing reflexes" exhibited by the decerebrate animal, and the tonic neck and limb reflexes of the residual hemiplegic human subject, although they present clear indications of their nature as tonic or postural reactions, are nevertheless caricatures of these reactions as they occur in the completely intact individual.

The question that arises is whether both the phasic and the postural components of co-ordinated movement suffer equally in this way in cerebellar ataxy. It is true that Rademaker found reactions of both types to be affected in his dogs, but we have only to consider the very intimate "co-operation of antagonism" existing between the two components to realize that a defect in one cannot leave the other unaffected.

It remains possible, therefore, that in the voluntary movements of the decerebellate dog the main defect is one of the postural component.

In a previous study of cerebellar ataxy, it was pointed out that the excessive range of movement, abruptness of onset and cessation of contraction, ill-sustained intensity of contraction and ready fatigue of the reflex contraction of muscles rendered atonic, either by de-afferentation or by spinal transection, are all qualities which we may detect in the muscular movements of cerebellar ataxy. In the latter, however, three factors seem to be in operation, impaired refinement and excessive intensity of postural activity complicated by voluntary efforts at correction. Upon this basis, therefore, we might suggest that cerebellar ataxy is not the result of a simple loss of postural activity, but of a disorder of this component of co-ordination of the kind just described, with the addition of voluntary efforts at correction. To the conception of cerebellar functions formulated above, namely, that the cerebellum is an organ through which the cerebral motor cortex achieves the synthesis of co-ordinated units which go to make up voluntary movements, may be added this further element of definition, that the cerebellum is the organ through which the cerebral motor cortex correlates the postural components with the phasic components of co-ordinated voluntary movement. If we employ Tilney's terminology we might say that *the cerebellum is the organ by which the cerebral cortex achieves integrative synergia in*

voluntary movement, and, conversely, that cerebellar ataxy is the expression of a defect of integrative syngeria in voluntary movement. In both definitions the voluntary element must be explicitly stated if they are to express the facts of observation accurately.

It is well to remember, however, that even if these generalizations should ultimately prove to be correct, they remain for the moment merely provisional definitions of a complex process which has not been analysed. The danger involved in the use of the terms "synergia" and "asynergia" is that they are apt to make us think that we have already penetrated the secrets of cerebellar functions and that nothing remains to be elucidated.

It is not necessary to stress the difficulties which must beset any attempt to verify this working hypothesis of cerebellar functions by the simple observations—either ocular or cinematographic—of the subject with cerebellar ataxy in whom we see nothing else than the algebraical summation of many component factors, each of which is itself hidden from us. Here the experimental worker, with his wide control over the conditions of his experiment, has opportunities which are denied to the clinical observer.

Of the localization of function within the cerebellum it is perhaps premature to speak before we know what is the function we seek to localize, but it may be remarked in passing that those who refer to the subject are invariably thinking of the quite distinct problem of the localization of symptoms of lesions within this organ. In this instance we have a field of clinical investigation which may yield information of great diagnostic value, even although we never penetrate the secret of cerebellar functions.

Dr. GORDON HOLMES regretted that time did not permit a further discussion on the interesting and important work that had been presented in the opening papers. These have furnished much new material on which it may be hoped that more complete knowledge of the functions of the cerebellum and of the symptoms that result from its disease may be based.

The discrepancies that still exist in even elementary observations, despite the large amount of work that has been devoted to the cerebellum, are remarkable. On the anatomical side, for instance, Sachs has found fibres of cortical origin entering the brain-stem and even the third nerves, while Mussen has described new tracts with cerebellar connections. On the physiological side Mussen has obtained, in contrast to the most reliable work hitherto published, local motor reactions by electrical stimulation of the cortex; and both he and Sachs regard the central nuclei as excitable, though Clarke in the latest summary of his work

with Horsley concluded that the reactions they observed were due to spread of the current to structures in the brain-stem. Even simple clinical observations are divergent. I may only point out that Weisenburg believes the leg is always more affected than the arm if both are involved, while in my experience the arm always suffers the more; and his clinical investigations have lead him to the conclusion that a more precise localization exists in the cerebellar cortex than I have ever found evidence of.

The most valuable facts that we have learned from this discussion seem to me to be that whatever the functions of the cerebellum may be, these functions have little influence on the reflex activities of the isolated brain-stem. This is obvious from the observations of Pollock and Davis, which in this matter are in general agreement with the earlier work of Sherrington, Magnus, Rademaker and others.

The only points on which time will permit me to touch are the nature of some of the motor disturbances that result from cerebellar disease, and the evidences of localization of function in the cerebellar cortex in man.

Tilney, Weisenburg and others have described the so-called ataxia of the cerebellar disease as an "asynergia," that is a disturbance during movement of the active association between the muscles primarily engaged and their antagonists. At one time I believed that such a disorder might explain some of the motor phenomena, but repeated investigations have convinced me that in man at least no such disturbances exist in sufficient degree to account for the symptoms. I have repeatedly examined, especially since the appearance of Tilney and Pike's paper, the relations of various groups of agonists and antagonists, both by direct observation and by graphic methods, but have been unable to detect any definite disorder in these relations. In this observation I am in agreement with the observations of Pollock and Davis on the normal activity of the so-called synergic units in the decerebrate preparation.

I believe, however, that in cerebellar disease the effect of contraction of a muscle, or of an associated group of muscles, may be irregular or inadequate to its aim owing to a disturbance or loss of tone in its antagonists. If, for instance, the contraction of the flexors of the elbow is not controlled by a normal state of tone in the triceps, the resulting movement may be irregular in rate and range; it is particularly liable to be excessive, so that the moving arm overshoots its mark and the phenomenon of hypermetria appears.

Despite some physiological observations, as those of Rademaker, there can be, in my opinion, no doubt that the tone of the muscles is

affected by cerebellar disease, and that this loss of tone bears a definite relation to the disorders in movement. "Tone" or "tonus" has been unfortunately used in different senses both by clinicians and physiologists; I apply it to the state of steady but varying contraction of the muscles that maintain a segment of the body at rest or in varying postures, especially during the movement of other parts on this segment. When, for instance, in a case of right-sided lesion of the cerebellum the arms are held out horizontally, the right arm swings more widely than the left when both are tapped, and if the observer while holding each arm by the forefingers shakes them about the passive excursions of the right are much greater; there is then obviously a defective fixation of the limbs at their more proximal joints. A similar lack of proper fixation at the distal joints can be demonstrated by seizing the forearm and shaking it. But perhaps the clearest clinical evidence of this defect of postural fixation is the swinging, pendular character of the knee-jerk which is frequently seen in cerebellar disease. This deficiency of fixation, owing to loss of the tonic contraction of fixating muscles, is an important factor in cerebellar ataxia. When, for example, the patient is asked to raise his arm vertically, the limb is liable to sway passively from side to side, owing to defective fixation by the shoulder muscles, or if the intended movement is horizontal the finger swing up and down irregularly, since the horizontal level is not accurately maintained by a regular tonic contraction of the elevators of the arm and other muscles. A defect of tone can, therefore, explain some of the disorders in movement; defective fixation permits passive oscillations, or fails to ensure the maintenance of proper posture and the alterations in the degree of contraction of the muscles which should counteract the varying force of gravity as a limb moves; and secondly, by the absence of the steadying influence that tonicly contracting antagonists offer to the movement of a segment of a limb by any group of muscles. I do not, however, claim that disturbances of tone explain all the motor disorders; there are undoubtedly other factors too.

The second point on which I will touch is the question of localization in the cerebellar cortex. There are, of course, two possibilities, that certain functions may be restricted to separate portions of the cortex, or that in the cortex there may be circumscribed representations of different portions of the body. In my clinical experience I have found no evidence in favour of either of these hypotheses. Most of the discussion has centred on the latter, that different portions of the body and the different segments of the limbs are separately represented in the cortex. I admit that the anatomical work of Bolk, as well as the morphological researches of Tilney and Riley and certain physiological

investigations support such a representation; but it is dangerous to deduce function from structure alone, and many of the stimulation and extirpation experiments are unconvincing or require confirmation The cinematograph demonstration by Mussen of his experiments, for instance, certainly suggested to me that the reactions he obtained were entirely due to spread of the current to the brain-stem and other structures.

My own conclusions are based on an extensive clinical experience and on the observation of more than eighty gunshot wounds of the cerebellum. I have also collected recently from the records of the National Hospital all cases of local lesions of the cerebellar cortex which were confirmed by autopsy, in which there were adequate clinical notes. Weisenburg has said most cases of local lesions recorded in the literature have been poorly studied, and this is my experience too, but in the National Hospital series there were about twenty cases on which arguments can be safely based. And in many of my gunshot wounds the lesions were undoubtedly small, circumscribed and limited to the cortex and the white matter immediately beneath it; this I confirmed by autopsy in certain cases, and it was most probably so in all in which a small portion of bone, with or apart from a missile, was merely driven a short distance into the cerebellum.

The examination of this exceptionally large material has lead me to the following conclusions on functional localization in the cerebellum: (1) Each lateral lobe influences the motor functions of the same side of the body only. (2) When the vermis is injured or both lateral lobes are involved, articulation and the postures and movements of the head and trunk are more affected than when one lateral lobe only is damaged. (3) No local lesion affects only or exclusively one limb or a portion of a limb.

It may, therefore, be that the vermis is chiefly concerned in the motor functions of the head and trunk, though these suffer equally when both the lateral lobes are involved, but there can be, in my opinion, no question of separate representation in the cerebellar cortex of the individual limbs.

Dr. KINNIER WILSON: Owing to time restriction I shall refer solely to one point in connection with cerebellar symptomatology.

The phenomenon of *skew deviation of the eyes*, comparatively rare though it is, has long been recognized as an occasional sequela of cerebellar disease, natural or artificial. In this condition one eyeball is deviated upwards and outwards, the other downwards and inwards, producing an ocular distortion of so striking a character as to impress itself on the observer. The late Sir Victor Horsley regarded it as specially

prone to occur after lesions of the middle cerebellar peduncle, although as a fact its anatomical basis has not been satisfactorily elucidated. Most of the cases in which it has come under my personal notice have been cerebellar tumours, naturally producing topical and distance effects which render precise localization of its mechanisms rather difficult.

Hughlings Jackson approached the problem from the physiological side, as he once explained to me. With strong convergence the eyes turn down and in; with extreme divergence they tend to turn out and up. He conceived that disease destroyed unilaterally a mechanism, linking homolateral convergence and contralateral divergence; the result of the outfall of this one of a pair of corresponding opposites was to bring about overaction of the other component, and so a more or less fixed attitude of skew deviation.

I too wish to approach the question from a physiological viewpoint. To understand my suggestion it is necessary to predicate the possibility of the eyeballs remaining fixed while the head as a whole—inclusive of the eye-sockets—moves, and vice versa. We know quite well that this is feasible for movements of head, or of eyes, separately in the horizontal plane, or in the vertical plane. The subject can fix his eyes on a given spot in front of him, while he allows the head to be passively deviated or turned, in the horizontal plane, to right or left, the result being deviation of the eyes in the opposite direction. Now conceive of the same occurrence when the head is passively tilted to one side, e.g., vertex towards the right shoulder, chin towards the left. If it were possible for the eyes to remain fixed on the given spot, but loose in and unconnected with the tissues of their sockets, they would then adopt an attitude of perfect skew deviation, which would result passively from the alteration of the position of the head to the oblique from the vertical. I have here a little toy animal so constructed that the eyeballs are completely fixed, though the whole head can be made to move separately from them, and if I tilt the head to one side, so that its long axis is oblique, the eyes are immediately seen to assume the posture of absolute skew deviation.

It is quite conceivable that the phenomenon represents an attempt on the part of the eyes to maintain the normal position in reference to external objects, when the head is thus altered in relation to space, and it is an easy step to reach the converse. For we may suppose that in pathological circumstances the head remains in its normal posture, and the disturbing element is acting on the eye mechanisms; in that case the latter are subjected to the "tilting," with the consequence that they adopt the position of skew deviation. Thus the suggestion is that skew deviation takes place when head is tilted and eyes are fixed; analogously, when head is fixed and eyes are "tilted."

The bearing of this question on the interesting phenomena described by Magnus and de Kleijn in respect of "righting" reflexes of head and of eyes will be obvious to the reader, but cannot be further developed for the moment.

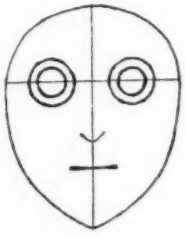

FIG. 1.

FIG. 2.

If the head and with it the eye-sockets are free to move round the axis at the point where vertical and transverse diameters cross, while the eyeballs themselves remain fixed on a distant point, then as the head is tilted the eyes come into the position of skew deviation. The ocular features are intentionally somewhat exaggerated in the diagrams, so as to bring out the change more satisfactorily.

SYMPOSIUM ON SENSORY DISORDERS IN ORGANIC DISEASE OF THE NERVOUS SYSTEM.

(1) DISTURBANCES OF SENSATION FOLLOWING SECTION AND SUTURE OF A PERIPHERAL NERVE.

BY JOHN S. B. STOPFORD, M.D., F.R.S.
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SINCE the publication of Head's experiment upon cutaneous sensation, there have been ample opportunities of testing his findings clinically, and furthermore, Trotter and Davies and Boring have also performed human experiments. In a review of the investigations by Trotter and Davies, who divided no less than seven nerves, Head has stated "the facts they observed correspond remarkably with those we have described." Boring in his one human experiment unfortunately selected a small nerve twig which on section produced such a diminutive area of defective sensibility in the fore-arm that he was hampered from the start, and when sensation commenced to recover was greatly confused. In spite of the very limited extent of the skin upon which he worked, Boring was able, however, to confirm some of Head's observations, and particularly that with respect to the more intense response to pain, heat and cold in the affected region during recovery, which he calls hyperæsthesia, and the phenomenon of "reference." Notwithstanding the agreement upon so many of the observed facts, neither Trotter and Davies, nor Boring, are prepared to accept the explanation submitted by Head. Instead of the division of cutaneous sensation into two systems, and the suggestion that the manifestations found in the intermediate zone are release phenomena, Trotter and Davies prefer to introduce "irritative changes" as an explanation, and Boring propounds a somewhat complicated theory to explain the observed facts. The essential part of this theory depends upon the existence of a multiple innervation of the individual sensory spots in the skin, which appears to have no anatomical foundation.

It is apparent from a perusal of Von Frey's papers that in the course of his many investigations he has noticed a number of the more

important observations stressed by Head and other workers. In an examination of Head's hand, he admitted that over an area where Head maintained there was a recovery of protopathic sensibility only, the heat spots when stimulated gave abnormally vivid responses, and yet the surrounding skin was insensitive to intermediate temperatures. Von Frey appears to believe that this overaction must be due to an abnormal irritability of the nerve fibres, although it is evident from his own work that he found a similar sensory state normally in the glans penis, where obviously he cannot suggest a pathological condition to explain the normal.

My own researches have convinced me that the existence of two systems in both cutaneous and deep sensibility can alone account for the observed facts, and it seems advisable to enumerate the principal reasons for this belief. For convenience, cutaneous and deep sensibility will be considered separately, and the former will be referred to first, since most workers have confined their attention to this alone.

(1) After division of a peripheral nerve of any size, a definite dissociation of sensation is demonstrable in the intermediate zone. In this region certain elements of sensation are lost and certain others retained; the former are concerned with the discriminative aspects of sensation and the latter with the protective. The reactions to stimulations (the painful prick of pin and extremes of temperature) which cause a response in this part are abnormal, being more intense and diffuse than over unaffected parts. In the intermediate zone the patient is unable to localize the painful, hot or cold stimulus, to judge its intensity, or to compare successive stimulations. The responses are of the "all-or-nothing" type, and heavily charged with affective tone.

(2) It occasionally happens, after division of a peripheral nerve, as in the triangle in Head's experiment, and invariably after section of the posterior roots of spinal nerves, that a complementary type of dissociation is encountered. Regions of skin are found where stroking lightly with a wisp of cotton-wool is appreciated, where fine differences in temperature are recognized, and where discrimination and localization of cutaneous stimuli are possible. On the other hand, the extremes of temperature and the painful prick of a pin, which are associated with the protective functions of sensation, pass unrecognized. Such dissociation is in every way the reverse of that found normally in the intermediate zone after division of a peripheral nerve. The occurrence of such complementary areas of dissociated sensation definitely indicates the existence in cutaneous sensation of two systems, which are

independent and not simply concerned with the modification of the same fibres and end organs. It is significant to notice that in each case two distinct groups of elements of cutaneous sensibility are affected, and that one group consists of elements concerned with protection, and the other with the higher discriminative functions.

(3) During recovery after successful suture of a peripheral nerve, two stages are invariably observed. During the first stage there is a return of the ability to appreciate the painful prick of a pin and extremes of temperature. With the completion of the first stage, the affected area is precisely like the intermediate zone after division of a peripheral nerve, and exhibits all the characteristic features. These features are never encountered unless the discriminative aspects of sensation are absent, which suggests that they are release phenomena. During the second stage of recovery, the other group of elements of sensation, concerned with discriminative functions, return. With their reappearance the features which have been described as characteristic of the first stage disappear. If, during the final period of recovery, the part be cooled, it is discovered that the discriminative elements of sensation disappear, and the accompaniments of the first stage at once return, demonstrating again the relation of the two groups of elements, and the probability of such features as overaction being release phenomena.

(4) In a proportion of cases of suture of peripheral nerves, particularly those of secondary suture, very incomplete recovery of sensation occurs. In an appreciable number under personal observation, recovery has not proceeded beyond the first stage, yet in such patients the part has exhibited the protopathic qualities for an indefinite period. In my experience there appears to be no limit to the time during which overaction can persist, and I have seen it continue without modification for ten years. The system concerned with protection usually recovers more completely, as well as earlier, than that associated with discrimination, and this is constantly the case after secondary suture. I have yet to see a perfect recovery of the discriminative elements of sensation after the latter operation.

(5) Studies of the normal sensory condition of the glans penis have shown conclusively that the cutaneous sensation of this region has exactly the same characteristics and peculiarities, excluding reference, as an area of skin in any part of the body at the end of the first stage of recovery. There seems to be no doubt that the skin of the glans penis is devoid of epicritic and endowed only with protopathic sensibility.

These observations must cause us to hesitate to allege that such conditions as the overaction found at the end of the first stage of recovery have a pathological explanation.

It is necessary now to refer briefly to deep sensibility, as I submit that there is strong evidence that the elements which Head has grouped together under this subdivision of sensation ought to be divided into two systems comparable to the two in the skin. Elsewhere [1] I have shown that during recovery after suture of a peripheral nerve deep sensibility also returns in two definite stages. During the first stage there is a return of the power to appreciate pressure pain and the mere contact of a pressure stimulus. The responses are of the all-or-nothing character, and the patient is unable to estimate the intensity of the stimulus or to localize the site of its application. Furthermore, the pain induced is more unpleasant and more vivid than that caused by the same amount of pressure on normal parts. The second stage consists of the recovery of the ability to localize a pressure stimulation accurately, and to recognize the position of joints and appreciate the extent and direction of passive movement. With the return of the ability to localize accurately, the unpleasant and unusually vivid responses to excessive pressure disappear, indicating that they are release phenomena. As in the case of cutaneous sensibility, recovery may be arrested at the end of the first stage; the second stage recovery is commonly incomplete after primary suture, and invariably so after secondary suture. In such cases the accompaniments of the first stage persist indefinitely and unchanged.

Thus in deep sensibility the elements of sensation concerned with protection and mere awareness recover first and more completely, while those associated with discrimination recover later and less perfectly—a state of affairs exactly similar to that found in a study of cutaneous sensibility.

On testing the sensation of the glans penis, which is subserved by subcutaneous end-organs, it is found that a pressure is appreciated, although cutaneous tactile stimuli are not recognized. If the pressure is increased sufficiently, pain of a very unpleasant character emerges rather suddenly. The patient is unable to estimate the intensity, and, in my experience, to localize accurately the point stimulated, if fallacies due to stimulation of surrounded parts are excluded. This seems to show that the subcutaneous tissues of the glans penis are endowed with only one system of deep sensibility, and it is important to notice that the vivid responses normally induced by excessive pressure

are like those encountered at the end of the first stage of recovery after suture of a peripheral nerve. The presence of protopathic qualities and this vivid response to considerable pressure, as normal reactions in this part of the body, appear to make it quite impossible to introduce irritation or imperfect repair as the cause of the phenomenon of overaction, which is constantly found at the end of the first stage of recovery in both cutaneous and deep sensibility.

Since there are such good reasons for believing that two exactly comparable systems exist in both cutaneous and deep sensibility—one composed of elements of sensation concerned with protection, and the other with discrimination—and since evidence has been submitted in some of my papers ([1] [2]) to show that it is rarely practicable to isolate the sensation of the skin from that of the deeper tissues, it appears justifiable to combine these two comparable systems and so procure a simple subdivision of sensation into two parts.

System I.—A system, composed of the protective elements of sensation, in which recovery occurs early and is more perfect, after suture of a peripheral nerve.

Recognition of :—
- (*a*) Pain (whether induced by prick or excessive pressure).
- (*b*) Extremes of temperature.
- (*c*) Tactile pressure.

System II.—A system, composed of the discriminative elements of sensation, in which recovery occurs at a later time and is less complete and perfect.

Power of :—
- (*a*) Localization.
- (*b*) Discrimination.
- (*c*) Recognizing position and passive movement.

Recognition of fine differences of temperature.

Appreciation of the lightest of touch.

With such a subdivision of the elements of sensation before us, it appears inevitable that our attention should be directed to the thalamus and the sensory cortex for a probable explanation of the existence of these two systems. When the conditions observed at the end of the first stage of recovery, after suture of a peripheral nerve, are contrasted with those found to result from an extensive lesion of the sensory cortex, which almost isolates or releases the thalamus from the sensory cortex, a central explanation appears to be still more attractive and probable.

The sensory cortex is concerned with the higher discriminative functions which are essential for the examination of objects by touch. It is necessary for the appreciation of all spacial relations, for the power to recognize similarity and difference, and for the recognition of stimuli of graduated intensity whereby we are able to distinguish differences in intermediate temperatures. After destruction of a considerable

part of the sensory cortex, stimulation with the finer tactile hairs is not recognized, since this requires a considerable amount of discrimination. Consequently it is seen that System II demands the normal functioning of the sensory cortex. The optic thalamus is a centre for awareness and is concerned with the protective, affective and non-discriminative aspects of sensation. Painful stimuli and the extremes of temperature mainly appeal to the thalamus, but although recognized in the absence of the sensory cortex, there is no power to compare sensations, estimate their intensity, or localize accurately the point stimulated. When released from cortical control, the thalamic response shows the typical "all-or-nothing" qualities. Furthermore, with release of the thalamus, there appears the characteristic overaction, the sensation being more vivid on the affected side, and radiating widely in the absence of the ability to localize. Thus it is seen that the elements of sensation composing System I make their appeal to the thalamus, and when they are released by a severe destructive lesion of the sensory cortex, the characteristic overaction becomes manifest—which is exactly similar to the condition found at the end of the first stage of recovery after suture of a peripheral nerve.

Such a central explanation for the existence of the two systems explains the sensibility of the glans penis, which seems to be endowed only with thalamic aspects of sensation, and it has also the added attraction of illustrating once again that the functions of the nervous system are integrated on the principles of evolution. If the thalamus and the sensory cortex provide a reason for recovery in two stages, it is possible, by reference to the conditions now known to prevail in a peripheral nerve after suture, to understand why a longer period must elapse before the fibres subserving the cortical forms of sensation function correctly, and why there is a less perfect and complete recovery of the discriminative than of the protective aspects of sensation.

Researches during the last ten years have proved the existence in all the large nerve-trunks of intraneural plexuses, which render it impracticable to procure perfect and accurate end-to-end apposition of the constituent nerve-bundles if there is any loss of nerve substance, which is inevitable in the case of secondary suture. Disturbance of intraneural pattern following suture provides one of the gravest limitations to this operation, and introduces a factor which cannot be fully controlled. It is well known that in consequence of the inevitable disturbance of intraneural pattern after suture, chance plays an appreciable part in the success of the result, since a variable number of

regenerating fibres may grow down into connective tissue and be functionally lost, whilst others may grow down heterogeneous paths in the distal segment. Afferent fibres may grow down to motor end-plates and efferent fibres may reach sensory end-organs, and it must be remembered that crossing of the fibres of the individual sensory paths may occur. Crossing of the fibres in the two different sensory systems must result in loss of function, but a consideration of crossing of fibres of the same system seems to shed light on the problem at the moment before us.

In an earlier paper [3] I have submitted evidence to show :—

(1) That heterogeneous connections within certain limits may be succeeded by recovery of the all-or-nothing response to pain, heat and cold. The adequate stimulus is dependent upon the type and condition of the end-organ, whilst the change in consciousness depends upon the central connections. Pain, heat and cold fibres reaching homogeneous end-organs in *any part* of the sensory field under investigation will function as soon as connections from end-organ to thalamus are re-formed in their full continuity.

(2) That heterogeneous connections in the case of fibres concerned with the higher aspects of sensation are not likely to be succeeded by any return of sensibility, either immediate or in the future. Fibres concerned with the higher aspects of sensation, such as spacial recognition in one, two, or three dimensions, may reach homogeneous end-organs without any recovery of function as discovered even by graduated tests, but it seems possible under these circumstances that by re-education some recovery may follow at a later date. The extent of the recovery under such conditions not only depends upon fortuitous regeneration, but also upon the educatability of the patient.

It is thus seen that the inevitable disturbance of intraneural pattern by cross connections leads to a much greater functional loss of System II fibres than in those of System I, and whereas in the case of the latter re-education is of slight consequence, in the former it is of great importance, and I maintain is mainly responsible for the difference in time of recovery of the two systems.

Consideration of the consequences of crossing of sensory fibres also offers an explanation of the phenomenon of "reference," which is not unfrequently encountered at the end of the first stage of recovery, and disappears with return of the power of localization. If a localization

fibre, which previously extended to an end-organ on the dorsum of the thumb, grows down on regeneration to an end-organ at the wrist, a stimulus will be at first localized at (or referred to) the old site. It seems probable that education and experience may ultimately correct this, but it will require time. Such an explanation has been criticized, since all qualities of sensation may be referred, but I fail to see that this really raises any serious objection. If a crossed localization fibre reaches a suitable end-organ in the midst of regenerated pain, heat and cold spots, it is likely that all three qualities of sensation will be referred, since its end-organ will be stimulated by applications in its immediate vicinity. Investigations at the end of the first stage of recovery shows that reference is only found at definite points, and the reference is always to some spot within the affected area.

In further support of these conclusions with reference to the great significance and importance of disturbance of intraneural pattern, two observations must be borne in mind. Firstly, after secondary suture, where it is necessary to excise a segment of the nerve before opposing the ends, the risks of disturbance of intraneural pattern are greatly increased, and it is found that after this operation the recovery of System II is much less complete than after primary suture, and I have never seen a perfect recovery of System II after secondary suture. Secondly, the recovery after physiological division of a peripheral nerve—a condition in which there can be no disturbance of intraneural pattern; the two systems recover concurrently, and the two stages always seen after end-to-end suture are invariably absent.

Therefore I submit the following conclusions:—

(1) That after division and successful suture of a peripheral nerve the recovery of cutaneous and deep sensation occurs in two stages.

(2) The explanation for the existence of these two stages is provided by reference to the functions of the thalamus and the sensory cortex, together with a recognition of the disturbances of intraneural pattern which are known to result from the operation of nerve suture.

(3) This central explanation not only accounts for all the observed facts and for the normal sensibility of the glans penis, but is also in accord with our knowledge of evolution of the nervous system.

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(2) SENSORY CHANGES IN SPINAL CORD AND MEDULLARY LESIONS.

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(*London.*)

MODERN investigation, clinical and pathological, has definitely localized certain main areas and tracts within the spinal cord as sensory in function, others as purely motor. Diseases which are limited to motor function, such as poliomyelitis, lateral and amyotrophic lateral sclerosis, do not therefore at present concern us. On the other hand, lesions of the posterior columns, of the antero-lateral and anterior columns, and of the central grey matter and posterior root zone, especially give rise to sensory changes of varying kinds, and the purpose of this paper is to introduce discussion on the sensory changes met with in various spinal diseases.

Transverse lesions from acute myelitis, gunshot and other injuries such as fracture-dislocation of the spine, need not perhaps detain us long, as in these cases usually the main interest is limited to a recognition of the upper level of the anæsthesia, so as to localize the level of the lesion in the cord. Gunshot or stab wounds may be limited to one side of the cord, or to the posterior columns, and may then afford useful evidence in the differentiation of function of the afferent spinal tracts. Similarly, in the slighter cases of myelitis, or in the recovering stage, differentiation of sensation is often met with, though little can be learnt from such cases as to the afferent tracts concerned.

Total anæsthesia to all forms of tactile, pain, pressure, vibration and temperature sensations, is rare in cord lesions except in the acute softening of transverse myelitis, in tumour or in wounds of the cord, or in fracture dislocation. In incomplete softening the sensory symptoms are slight and are overshadowed by the motor paralysis. Pain and temperature may be more involved than tactile sensation, and frequently the Brown-Séquard syndrome may be more or less completely demonstrable.

Hyperæsthesia to touch, pain or temperature is not unfrequently met with at the upper level of the anæsthesia due to acute transverse lesions, or in pressure paraplegias, and may be due to irritation of the

posterior root zone within the cord, or of the posterior roots. A curious alteration of localization which has been reported in a few of such cases is the reference of all painful stimuli applied to the lower limbs and sacral areas, to the level of the hyperæsthetic zone.

The forms of sensation with which I propose especially to deal are :—

Tactile, light touch, as with a camel's hair brush. *Quality*, e.g., discrimination between silk, wool, velvet.
Localization of touch.
Cutaneous pain, e.g., pin-prick, faradic wire brush.
Compass, discrimination between one and two points.
Thermal, heat and cold.
Passive position of limbs and joints.
Sense of form, recognition of objects.
Pressure, *Pressure pain* } Deep sensibility.
Weight discrimination.
Vibration.

All the stimuli which ultimately produce these various sensations reach the spinal cord by the posterior roots, and consequently in *tabes dorsalis* any or all of these different forms of sensation may be affected in various degrees.

Lightning or shooting pains, sometimes boring in character and often described by the patient as "rheumatic," are one of the earliest and most frequent signs of the disease, and hyperæsthesia of the skin is sometimes found temporarily in the area of these pains, though a firm grasp is easily borne, and even a hard grip of a muscle, such as the calf, may be painless, though extremely painful in a normal individual. Girdle pains, too, are not uncommon. Analgesia is frequently an early sign, and is likely to be found on the outer side of the leg or the fifth lumbar segment, the front of the chest over the third to sixth dorsal areas, and on the inner side of the fore-arm on the first dorsal area. The analgesia may be widespread long before equilibrium is affected, and there may be no trace of ataxy. Sir John Rose Bradford once told me of the case in a man whose earliest sign of disordered nervous action was that he noticed when taking his morning bath that he could scrub himself all over his chest with a nailbrush without any discomfort. Such cases with widespread analgesia may be mistaken for syringomyelia in the early stages. In a young woman, aged 28, admitted into hospital for "gastric ulcer," but suffering from typical gastric crises,

I found universal analgesia, excepting the mask portion of the face, though she had no sign of ataxy and all the deep reflexes were brisk. Typical Argyll Robertson pupils were present, and an interesting point in her history was the fact that of four children she had had, the first two births were associated with the usual pains of labour, though with her last two children there had been no pains of any kind, indicating the development of uterine anæsthesia. Genital anæsthesia with impotence is often an early sign, and retention with incontinence both of bladder and bowel. Loss of testicular sensation is sometimes met with, and other deep parts such as joints may be analgesic, so that acute disorganization of a joint in Charcot's arthropathy may be altogether painless. This is not always so, however, and a painful Charcot's joint may be associated with complete analgesia of the skin overlying the joint.

Areas of skin which are analgesic to ordinary pin-prick may be very sensitive to a scratch, due perhaps to summation of stimuli. This phenomenon of excessive sensitiveness to scratch over an area where tactile sensation and pin-prick are diminished, may be seen in the stage of protopathic recovery of an injured nerve. Probably it is owing to this summation of stimuli that the abdominal reflex is often quite brisk, although the skin may be analgesic to pin-prick.

Paræsthesiæ of tingling, numbness, or formication in the legs are common, as is also the sensation as if the feet were standing on cotton-wool or india-rubber. Often the soles of the feet are almost normally sensitive to touch and prick, though ataxic gait is marked. Subjective sensations of cold, especially about the legs, are very common in tabes, and such patients are extremely sensitive to draught, and are inclined to wrap their legs up in a rug even in warm weather. Hyperæsthesia to cold, *psychroæsthesia*, is commonly met with in this disease, and a cold piece of metal applied to the skin, especially on the abdomen and lower chest, may be violently discomforting to a tabetic patient, although this area may be analgesic to pin-prick and insensitive to ordinary degrees of warmth. Hyperæsthesia both to cold and to heat may be present on areas of skin which are analgesic to pin-prick.

In *hereditary ataxy* or Friedreich's disease, and in the various forms of cerebellar ataxy, tactile sensibility and sensation to pin-prick and thermal stimuli are usually unaffected, except in the later stages of the disease, when partial loss of all these forms may be met with. Loss of sense of position, particularly of the toe joints and ankles, may be present, but it is especially the muscle sense that is affected in this disease. Pains are usually completely absent.

Combined sclerosis may be subacute or chronic. In the latter form spontaneous pains are usually absent, though I have known them severe and lancinating, resembling mild tabetic pains, in the case of a man who thirty years before had been exposed to a severe chill and exposure when shooting. Pains commenced immediately afterwards, followed by very slow development of weakness of the legs and slight unsteadiness, with extensor plantar reflexes. Syphilis could apparently be excluded, as the Wassermann test was negative.

In the subacute form of the disease vague pains, paræsthesiæ and objective sensory disturbances are usually seen. Profound loss of sense of position in the limbs is likely if posterior sclerosis is extensive. Hyperæsthesia may be present at the same time to pin-prick and to heat, without any temperature loss. Loss to compass test and appreciation of weights may also be found.

Disseminated sclerosis may be contrasted with tabes dorsalis in that the latter produces sensory disorders through disease of the posterior root fibres before their entry into the spinal cord, while in the case of disseminated sclerosis the lower sensory neurones are intact, and it is only after the re-arrangement of the sensory impulses in their intra-spinal and cerebral tracts that they meet with obstruction in their upward path. Islets of sclerosis may invade all parts of the white or grey matter of the spinal cord, quite irrespective of the anatomical relationship of the tracts, and similar distribution of the patches of disease is found within the brain in the medulla and pons, basal ganglia and central white matter, though they are likely to be much scarcer in the grey cortex. Consequently, the early symptoms vary enormously, and the initial signs may be either of cerebral or spinal origin. There may be a hemianæsthesia and loss of sense of position in the limbs, or a unilateral numbness without any objective loss of sensation to touch, pain or temperature, or to vibration. Sensory symptoms referable to spinal areas of sclerosis in this disease may be various in nature. Numbness is one of the commonest, though objective tests may fail to demonstrate any tactile pain or heat loss. Paræsthesiæ, such as pins and needles sensation in one hand, arm or leg, sometimes tingling or vague pains, are fairly common; these latter rarely are severe, stabbing, boring or dragging in character in the extremities, or around the trunk with a girdle sensation of constriction. Fugitive shifting paræsthesiæ are very characteristic and of high diagnostic value.

Vibration loss is very inconstant, and in a minority of cases there may be demonstrable diminution to touch and pin-prick on the ex-

tremities, though never in defined segmental areas. Agnosia or loss of the stereognostic sense may accompany loss of the sense of position in the extremities. In a man, aged 51, the first sign of nervous disease was inability to distinguish coins in his left trousers pocket. Total loss to all forms of touch, pain and vibration at the same time, is probably never met with in the disease, though complete vibration loss on one or more extremities is not common. Hysterical phenomena in the course of disseminated sclerosis is a frequent source of difficulty in differential diagnosis. Thus, a single woman, aged 42, had for five years increasing weakness of the left leg, difficulty in controlling the arms, followed by ataxic utterance, diplopia and incontinence of urine, and coarse rotatory nystagmus. The left leg was rigid in extension, but could be passively flexed with the use of considerable force; there was complete loss of power in the left ankle, with foot-drop, and total anæsthesia of the whole of the left lower extremity below the middle of the thigh. The flexor fore-arm and flexor finger-jerks were much exaggerated, but the knee-jerks were weak, there was no ankle-clonus, and the plantar reflexes were flexor, but the abdominal reflexes were absent. It seems impossible to explain this bizarre condition except by a combination of hysteria with organic disease.

Pain referred to the fifth nerve may be tingling and burning in the face and side of the tongue, with partial loss to tactile and painful stimuli. A typical case of disseminated sclerosis, a woman, aged 43, developed numbness of the left upper and lower jaw and half of the tongue, and complained of loss of taste, that "everything tasted like bran mash." Such symptoms may be due to a patch of sclerosis affecting the trunk of the nerve at its exit from the pons, as Oppenheim has described, or by a lesion involving the principal sensory nucleus of the fifth nerve within the pons.

More difficult to understand is the special association of *chronic paroxysmal trigeminal neuralgia* with disseminated sclerosis. The neuralgia may be bilateral or unilateral; in several of the twenty-three cases of typical chronic trigeminal neuralgia that I have seen associated with a chronic spastic paraplegia, the majority of which were undoubtedly cases of disseminated sclerosis, the neuralgia was bilateral, a proportion of bilateral cases many times higher than is met with in uncomplicated chronic trigeminal neuralgia, in which the bilateral cases amount to about 5 per cent. My explanation of the association of this neuralgia with disseminated sclerosis is as follows: The type of pain is precisely that of ordinary chronic trigeminal neuralgia, with trigger

zones, and it is brought on by eating, talking, or handling the face. It moreover behaves in exactly the same way as the ordinary form of tic douloureux to alcohol injection, and there is never any trace of anæsthesia or analgesia previous to injection.

It is true that spontaneous stinging pains in the face may be met with in chronic lesions of the pons or medulla affecting the nuclei or roots of the fifth nerve, as in syringobulbia, and in old cases of thrombosis of a posterior inferior cerebellar artery in which the spinal root of the fifth nerve has been involved. In these cases, however, there is always detectable anæsthesia or analgesia of the face, and the pains are in no way produced by eating or by handling the face, as in chronic trigeminal neuralgia. It is therefore difficult to resist the conclusion that the trigeminal neuralgia met with in disseminated sclerosis, apart from those exceptional cases where there is an actual patch of disease invading some part of the fifth nerve or its connections, is peripheral in origin, as in ordinary chronic trigeminal neuralgia. Probably the reason for its especial frequency in disseminated sclerosis, as opposed to other forms of chronic nervous disease, is that the spinal root of the fifth nerve, carrying the fibres for painful and thermal impressions from the face, is likely to be rendered hypersensitive by the presence of one or more patches of sclerosis in its near neighbourhood in its course through the pons and medulla, and this would also explain the unusual frequency of bilateral trigeminal neuralgia in this disease. Thus, a double cause is at work, a septic degenerative neuritis of peripheral nerve filaments in the jaw, and an irritant hyperæsthetic effect of islets of sclerosis in the medulla and pons in the neighbourhood of the spinal roots of the two fifth nerves.

The most striking changes that are found in chronic diseases of the cord are met with in *syringomyelia*, *intramedullary* and *extramedullary tumours*.

Pains in the back and limbs may sometimes precede for years any sensory or motor symptoms in these conditions. In a case of syringomyelia following an old acute anterior poliomyelitis, I have known chronic pains in the mid-dorsal region precede for seventeen years the development of typical syringomyelic symptoms. Many sufferers from syringomyelia complain of pain throughout the course of the disease, while others never appear to suffer any pain. Indeed, the absence of all pain, both spontaneous or due to wounds, injuries or burns, has been responsible for individuals who were really subjects of latent syringomyelia being hailed as heroes. In syringomyelia the damage done by

the gliosis in the posterior horn and central grey matter is apt to interfere with the fibres carrying painful and thermal stimuli without damaging to any appreciable extent those serving tactile sensibility. Those fibres in the posterior roots carrying pain and temperature sensations end in nerve cells in the grey matter of the posterior horn, and thence new axons carry these sensations in separate paths, decussating within four or five segments in the anterior white commissure to turn upwards in the spino-thalamic tract to reach the fillet in the medulla, finally ending in the thalamus.

The work of Head and Holmes, Spiller and others, has done much to clear up the apparent anomalies of sensory conduction within the spinal cord and brain-stem.

Tactile impulses cross in the cord much more slowly than those for pain and temperature, to run upwards in the anterior columns; therefore there are two paths available for a long time, one on each side of the cord, and consequently tactile sensation is less frequently completely abolished. Ultimately, all the tactile impulses decussate to the opposite anterior columns. Thus it is that in syringomyelia tactile sensation commonly escapes, though in my experience I have generally found that areas of skin in this disease which show well-marked analgesia and thermanæsthesia also show inability to discriminate the finer qualities of touch, such as distinguishing between silk and velvet. Though the lightest touches of a camel's hair brush may be perceived, yet the patient at once acknowledges that the touch sensation is not quite the same as on a normal area of skin. Usually the areas of cutaneous loss to painful and thermal stimuli correspond, but this is not invariable, and occasionally areas of analgesia may be almost normally sensitive to thermal stimuli, while again areas insensitive to cold may be normally sensitive to all degrees of heat. These facts go far to prove that the paths for pain, heat and cold, though running close together in the spino-thalamic tract, are yet differentiated from each other. Syringomyelic lesions may for years be unilateral, and yet may extend vertically for a considerable distance through the cervical cord to the lumbar enlargement. Root fibres entering the posterior horn will therefore be damaged in a great number of segments, and wide areas of analgesia and thermanæsthesia will be present on the same side as the lesion, and on the same side as muscular wasting, when present. Such wasting may be only of one side of the tongue, due to a syringobulbia invading the medulla and damaging the hypoglossal nucleus, yet analgesia may extend down the same side from the second cervical segment to the lower lumbar. Thus,

in a case under the writer's care, there is coarse nystagmus to the right, with hemiatrophy of the right side of the tongue, and analgesia and thermanæsthesia of the second, third and fourth cervical segments, from the vertex down the back of the head, including the neck as low as the clavicles on both sides. No analgesia is present on the hands and arms, but on the right side the analgesia commences again at the third rib and is continued downwards on the trunk and front of the thigh and leg, from the third dorsal to the fifth lumbar areas inclusive. The sacral areas are normal. Clearly in this case the lesion extends in the posterior horn from the level of the upper medulla to the fourth cervical segment on the right side, catching the decussating fibres from the upper cervical segments of the left side. The main cervical enlargement has not suffered from the gliosis, but the disease commences again on the right side at the third dorsal level and continues down to the fifth lumbar. The fillet has evidently not suffered in the medulla, and the medullary lesion is not extensive enough to cause the Brown-Séquard syndrome.

Recognition of passive position and of movement, and the recognition of the compass test, pass upwards in the posterior columns on the same side, not crossing until after passing through the posterior column nuclei. These sensations therefore usually escape damage in syringomyelia, as does also the appreciation of vibration and sense of position. In certain cases, however, of syringomyelia in which the destruction of the posterior horn and of the posterior root zone is extensive, there will be found total anæsthesia to touch and pressure, as well as to heat and cold and to pain, and with this loss there may be also loss of sense of passive position and of vibration sense.

Persistent pains in one area of the trunk or limbs is so commonly an early sign of intramedullary gliosis, before any muscular wasting or even before analgesia or thermanæsthesia can be detected, that the possibility of such aching, boring, burning neuralgias being due to this form of chronic spinal disease is perhaps hardly sufficiently insisted on. The sensation of pins and needles is less common in syringomyelia, but was present in a woman who for twelve months noticed pins and needles on the right side of the back of the neck and shoulder, with numbness and loss of sense of position. In a man, aged 61, there had been burning pain in the right foot for six months, with complete analgesia and loss of distinction of compass points below the right knee, and diminished sense of vibration. A lady, aged 49, had for four years complained of neuralgia at the back of her neck, extending

to the top of the head and forehead on the right side, usually waking her at 4 a.m. Cold became unrecognizable as such on the left hand, but produced an irritant effect, as though it burnt her. There was marked analgesia on the left leg and thigh, but heat and cold were unaffected in that region. A lady, aged 63, had for four years burning pain in the left foot, which she used to put into ice-cold water for relief. Thermanæsthesia gradually developed on the left lower extremity and trunk up to the seventh dorsal level, and the right leg became spastic, with an extensor plantar reflex, the Brown-Séquard syndrome. Vibration sense was totally lost on both lower extremities and the lower part of the trunk. There was profuse sweating of the left foot at times.

Inversion of temperature sense to cold may be observed, cold giving a sensation of strong warmth, and, as already mentioned, it may appear to burn. In another case there may be intense hyperæsthesia to cold, *psychro-æsthesia*, already described as being not uncommon in tabes dorsalis.

The following case illustrates several forms of sensory disturbance produced by the acute development of a syringomyelic fissure or a hæmorrhage into a cavity on one side of the cord. A lady, aged 62, already referred to as the subject of old acute poliomyelitis of the left hand and leg, had suffered for the past seventeen years from spasmodic attacks of pains at the back of the neck and head and under both scapulæ. Gall-stones had been diagnosed and the gall-bladder and appendix removed, without any improvement. Following immediately upon a trifling operation under an anæsthetic, she lost all remaining power in the left lower limb and noticed intense numbness of the left side of the trunk, and blisters were produced by a hot bottle on the right leg and thigh. On examination there was now found total anæsthesia of the skin to touch, pin-prick and pressure on the left side from the third dorsal level down to the ninth, though deep pressure on this side produced pain. On the right lower extremity there was complete analgesia to pin-prick and loss to heat and cold up to the seventh dorsal level, but cold metal applied to the left side below the eighth dorsal level produced intense discomfort, being felt as excessively cold. The right plantar reflex was extensor in type, though there was no trace of weakness of the right leg. The left plantar could not be tested, owing to amputation of the leg just below the knee having been done at the age of 15, owing to trophic disturbances and ulcers. In addition, the acute fissure or hæmorrhage on the left side

of the cord had either destroyed or temporarily abolished all function in the posterior root zone between the levels of the third and ninth dorsal segments, giving rise to total anæsthesia to touch, prick and temperature and to pressure touch. Deep pressure upon the abdomen on the left side of the middle-line caused pain, though equal pressure on the right side caused no pain at all, indicating that the lesion on the left side of the cord in the upper dorsal region had interrupted the conducting tracts for deep as well as for cutaneous sensations from the right leg and side.

It is often hard to distinguish between syringomyelia, intramedullary and extramedullary tumours. The Brown-Séquard syndrome has been quoted as evidence in favour of the diagnosis of extramedullary tumour as opposed to intramedullary gliosis, and, as applied to chronic syringomyelia this is mainly true, though, as has been seen, the Brown-Séquard syndrome may be quite typical in some respects in acute lesions in syringomyelia. In slowly developing intramedullary gliosis, whether it is of the nature of syringomyelia or gliosarcoma, the thermanæsthesia and analgesia are segmental, and are found upon the same side as the spastic palsy, which latter is usually slight in chronic gliosis, though sooner or later the paraplegia is the most prominent symptom in tumour. Total anæsthesia of a limb or part of a limb may be found in syringomyelia, but total anæsthesia of both lower extremities and the lower trunk is never found in this disease.

In cases of pressure paraplegia, as from extramedullary tumour or caries, motor paralysis may be much more marked than the sensory loss. In a recent case, under my care, a woman, aged 42, with gradual increasing paraplegia for the past three years, the motor paralysis of the legs was nearly complete, only weak movements of the toes and ankles being possible; but there was only slight anæsthesia on the legs and lower abdomen to all forms of sensation, the lightest touches being recognized and localized, and the recognition of pin-prick and of temperature being normal above the xiphisternum. A lipiodol X-ray photograph, however, clearly showed obstruction at the level of the lower border of the third dorsal vertebra, where, at the subsequent operation, a fibroma the size of a large almond was found compressing the cord on its dorsal surface, several segments above the highest level of the anæsthesia, which did not extend above the seventh dorsal level. Elsberg has shown that in extramedullary growths the loss of sensation spreads upwards from the feet, while in intramedullary tumours the loss may first be noticed on the trunk, and later on the lower extremities.

In the spino-thalamic tracts in the antero-lateral columns the most caudal fibres lie externally and posteriorly while those serving higher areas of the limbs and trunk are placed in a lamellar arrangement nearer the grey matter, more internal and anterior. Thus extramedullary tumours compressing mainly the dorsal and posterior fibres of the spinothalamic tracts cause greater anæsthesia on the feet, but in the case of a tumour compressing the cord on its ventral surface sensibility may be undisturbed in the most caudal segments. For example, a young man, aged 28, under my care, developed rapidly pain in the left arm with weakness, muscular wasting, and marked fibrillary tremors, the paralysis being chiefly of the deltoid, biceps, and other muscles served by the fifth cervical segment. At the same time there was spastic paralysis of the leg on the same side, with increased reflexes, and complete analgesia and thermanæsthesia of the opposite lower extremity as high as the groin only, sensation above this level being normal on both sides. To illustrate the converse proposition, a lady I have seen in consultation on two occasions lately, after suffering for six months from severe pains in the back, has within the last three weeks developed spastic paraplegia commencing in the left leg, and has now complete motor paralysis of both legs with retention of urine. Anæsthesia is well marked on the fronts of the limbs and on the trunk, ending sharply above at the upper border of the eighth dorsal level, but there is no detectable anæsthesia either to light touch, pin-prick, or to temperature on the backs of the calves, thighs, and buttocks, that is over the second and lower sacral areas. This distribution would correspond to Elsberg's description of pressure on the anterior surface of the cord at the eighth dorsal segment, which is very probably the case here, as she suffered in childhood from caries of the spine at a different level. X-ray photographs have as yet indicated no lesion in the spinal column to correspond with the present paralysis.

Syringomyelic sensory dissociation is often seen in extramedullary tumours; the appreciation of pain may be more affected than the temperature sense, or vice versa. This was so in a boy, aged 17, under my care during the past four months. He had numerous large neurofibromatous tumours in the skin, and five years ago developed a left facial palsy and hemiatrophy of the tongue on the left side. Five months before I saw him this spring he developed a slight left hemiplegia, with general weakness of the left arm, a limping gait and extensor plantar reflex. Three weeks before I saw him gradual weakness of the right wrist and fingers was noticed. There was no weakness

of the right leg or alteration of its reflexes, but marked analgesia with loss of temperature was present on the outer sides of both fore-arms, tactile sense being normal. Very gradually he became weaker, until he was completely paralysed and incontinent. At the autopsy numerous neurofibromata were found affecting the central nervous system, one on each side of the cervical cord at the second cervical level being clearly the cause of the progressive quadriplegia.

At the level of the posterior column nuclei in the medulla, those fibres carrying deep sensibility, except pressure pain, postural sense, spatial and weight discrimination, and vibration sense, which have travelled up the posterior columns on the same side, with the fibres serving tactile sense which have not hitherto decussated, all end in the posterior column nuclei, and are relayed upwards after decussation in the median fillet of the opposite side. They end in the ventral surface of the lateral nucleus of the thalamus. Within the brain-stem it seems reasonably certain that these fibres retain in the median fillet their separate arrangement, those for pain and temperature running lateral to those for touch and deep sensibility. Within the medulla and pons the fillet receives further accretions of afferent fibres from the sensory nuclei from the fifth, seventh, ninth and tenth cranial nerves. According to Freeman sensory fibres belonging to the exteroceptive system of the seventh, ninth and tenth nerves join the spinal root of the fifth nerve, while their interoceptive or visceral fibres end in the solitary bundle, with its attendant nuclei. He gives good reasons, based on the comparative anatomy of birds and fishes, why this nucleus of the solitary bundle is not gustatory in function, as Nageotte described, but is largely connected with respiratory movements.

The fifth cranial nerve, like the spinal posterior roots, divides on entering the pons into two main bundles, the upper serving tactile sensibility, while the fibres for pain and temperature turn downwards in the spinal root. Clinico-pathological experience, by Spiller, Head and Holmes and others, has demonstrated that the mandibular fibres terminate highest in the substantia gelatinosa, while those of the ophthalmic division pass further down the spinal root, a fact explicable on developmental grounds that the circumoral region is the most anterior portion of the organism. Numerous cases, moreover, of syringobulbia have been described in which the zones of analgesia are successively arranged on the face from behind forwards, leaving the nose and mouth as the last area to be involved. Pressure touch and pressure pain are, according to Davis, Ivy and Johnson and others,

conveyed by the facial nerve and not by the fifth nerve, on the analogy of Head's description of deep sensibility being conveyed not by cutaneous nerves but by fibres running with the motor nerves. Maloney and Kennedy, however, concluded that the fifth nerve conveys all pressure touch sensation, though after gasserectomy pressure pain may persist unimpaired in the face and tongue, but never in the eye. They add that the seventh nerve contains no pressure sense fibres distal to the Fallopian canal, but that sympathetic fibres subserve a general crude sensibility to pressure pain. I can fully confirm the statement that the fifth nerve conveys deep pressure sense, from my results of alcoholic injection of its second and third division and of injections of the ganglion. There cannot be the slightest doubt that total anæsthesia to hard pressure results from a well-placed alcohol injection of these nerves, or of the ganglion, whereas in cases of facial paralysis of Bell's palsy no detectable sensory loss is as a rule to be observed.

Lesions of the *medulla* are liable to produce sensory symptoms through damage to the sensory paths on one or both sides, and unilateral lesions may produce crossed anæsthesia due to the involvement of the fillet and one or more sensory cranial nerves on the same side.

Thrombosis of one posterior inferior cerebellar artery usually involves the spinal root of the fifth nerve and part of the sensory path on the same side, producing analgesia, thermanæsthesia and sometimes slight numbness and tactile loss on the trigeminal area on one side, with analgesia and thermanæsthesia on the opposite side of the body, including the back of the head and neck as far forwards as the trigeminal area on that side. Sometimes this analgesia extends further forwards from the back of the head as far as the hair-line, or even mid-forehead, excluding only the "mask," as already mentioned in syringobulbia

Lesions in the upper part of the pons may damage the sensory nucleus of the fifth nerve, together with the fillet on that side, but without injuring the spinal trigeminal root, producing what has been called the inverse syringobulbic type of anæsthesia, namely loss of touch without any loss of pain or temperature sense on the trigeminal area, associated with analgesia of the opposite half of the body, including the face. Such cases have been described by Spiller, Herringham and Hinds Howell, myself and others. After terminating in the upper sensory nucleus or in the substantia gelatinosa of the spinal root, all these fibres are then relayed by decussation to the neighbourhood of the opposite median fillet, but run more centrally as the trigeminal fillet to

end in the thalamus. Thrombosis in the tegmentum of the upper part of the pons may involve the fillet on one side, without any motor paralysis, and I have seen total hemianæsthesia from this cause, so intense that when the man was lying in bed on his right or anæsthetic side, he felt as if suspended in the air with the bed-clothes lying upon him. Such a lesion may cause bilateral ageusia, which appears to indicate that the gustatory fillet must run very close to the median line on each side. Lesions of the *thalamus* have been studied by Roussy and Dejerine, Head and Holmes and others, and the now well-known thalamic syndrome has been divided into sub-groups. Broadly speaking, it consists of partial hemianæsthesia, with greater loss of postural and spatial sensibility than of touch and pain, and little or no hemiplegia, but with hemiataxia and athetoid movements or hemichorea, and persistent paroxysmal, spontaneous pains on the affected side. It is particularly lesions of the posterior portion of the lateral nucleus, in which the median fillet ends, that produce this syndrome. Head and Holmes also describe an excessive reaction to painful stimuli, whether pressure or temperature tests were employed. Roussy called this symptom a "dysæsthesia," and described excessive reaction to pin-prick, to stroking the skin or the hair, or even to touch. This particular form of dysæsthesia is, in my opinion, strangely reminiscent of the character of the pain in causalgia, resulting from gunshot injuries of the nerves, and also in some cases of post-herpetic neuralgia. Section of the nerves in causalgia and of the posterior spinal roots in post-herpetic neuralgia has often failed to influence or to abolish the pain in these conditions, a point which is difficult to understand unless a central disturbance of function has been set up either in the grey matter of the posterior horn, or in the thalamus.

(3) DISORDERS OF SENSATION PRODUCED BY CORTICAL LESIONS.

BY GORDON HOLMES.

(London.)

It is generally recognized that the investigations of Sir Henry Head introduced a new era in our study of the disorders of sensation produced by cortical lesions. It is true that for years before 1911, when Head's first paper written in collaboration with Holmes appeared, many clinicians had studied the sensory alterations associated with cerebral disease and had described disturbances in various modalities of sensation, but the majority were satisfied with determining the state of cutaneous and deep sensibility in the cases they investigated, or correlating with an anatomical lesion a hemianæsthesia or a more restricted or a local loss.

Head, on the other hand, started his investigations with the question: What qualities of sensation are localizable in the cerebral cortex? And it was only when he obtained an answer to this question that he attempted to connect certain forms of sensory disturbance with pathological lesions of certain zones of the cortex.

It is necessary, if we wish to test Head's conclusions, to select cases in which the disease is limited to the cortex, and in which it is of such duration that all the effects of shock and other indirect disturbances due to the lesion have passed off. A failure to observe these precautions is probably the explanation of the "hemianæsthesia" and the gross disturbance of sensibility to touch, pain and temperature, still frequently described with cerebral lesions. Another factor, however, is the presence of hysterical phenomena in addition to, or even apart from, the cortical loss of sensation. Babinski has drawn attention to the ease with which an anæsthesia can be produced by suggestion in suggestible subjects, and many patients with cerebral disease fall into this category. During and since the late war, I have been impressed with the very frequent association of hysterical anæsthesia with gunshot wounds, and in my experience it is not uncommonly found with vascular and other lesions of the brain.

When these precautions are taken there can be no difficulty in confirming the general truth of Head's conclusions, though further investigation may modify or add to them. We have not worked together since 1914, but I had the opportunity of examining sensation in very large numbers of men with gunshot wounds of the cortex both during and after the war, and I have been able to investigate sensory disorders of cortical origin due to many other causes too. The results of my independent investigations accord closely with Head's latest conclusions.

It has been argued, as Marie, Bouttier and others have done, that the methods we employed are not suitable for ordinary clinical work, and that they may even be a source of error. Such a view can be due only to unfamiliarity with our methods, as each test we employed was devised to present the patient with the simplest task possible; in fact we found no difficulty in applying them to patients of even a low grade of intelligence, provided they were not pathologically dull. To the observer, too, they offer little difficulty; all can be easily employed at the bedside, except perhaps von Frey's hairs and other measures of tactile sensibility. Further, if employed for purposes of diagnosis only they require little time, though the complete investigation of a disturbance of sensation of cortical origin requires more time than the clinician can usually spare in routine work.

The first, and one of the most important, conclusions to which Head and Holmes came was that the "optic thalamus is the centre of consciousness fo rcertain elements of sensation," or, as Head later expressed it, "the seat of the physiological processes which underlie crude sensation of contact, heat and cold, together with the feeling-tone they evoke." As a corollary to this it is obvious that certain forms of sensation are never abolished, though they may be modified, by cortical lesions.

This is particularly true of *pain sensibility*, which is that form least altered by disease limited to the cortex. When the lesion is stationary there is no raising of the threshold to a pinprick or to any other painful stimulus, and if the anatomical lesion is small there is no difference apparent to the patient between the sensations evoked by similar painful stimuli applied to the affected and the normal side. Frequently, however, the patient states that the stimulus is "plainer" or "sharper" on the normal side, though if intelligent he may admit that it is not more painful. This is particularly so when a pin-prick is employed, and it is undoubtedly due to the better appreciation on the unaffected side of the sharpness or pointed nature of the pin. When, however, the lesion extends deeply into the white matter of the brain, the threshold to painful stimuli may be raised.

All my later experiences conform to this view; I have never found a pronounced hypalgesia, or raising of the threshold to pain, provided no subcortical lesions were present and that the effects of shock had passed off. Analgesia or a definite diminution of sensibility to pain is, however, still frequently described as a result of cortical disease. Goldstein, for instance, admits that it may occur, though it is usually less pronounced than the loss of other forms of sensation, and Pierre Marie and Bouttier assume that the cortex is largely concerned in the perception of pain. It is not easy to explain these discrepancies; in certain cases described the lesions were probably not purely cortical, or were accompanied by disease in the internal capsule, thalamus or deeper parts of the brain; in others the effects of shock or of recent epileptiform attacks may have been present; or it may be that an unrecognized hysterical anæsthesia complicated the organic picture, but it is probable that in many instances a mere subjective disturbance, unaccompanied by any alteration of the threshold, was interpreted as a hypalgesia.

Thermal sensibility is also as a rule little affected by pure cortical lesions, but the neutral zone may be slightly enlarged in comparison with the corresponding normal part, or when temperatures near the neutral zone are employed the sensations of heat or cold they evoke are less plain or distinct. Head emphasizes the difficulty the patient may have in distinguishing minor degrees of heat or of cold, and my independent experiences point to the same conclusion. Many reliable observers have recorded severe degrees of thermanæsthesia associated with cortical disease, but the explanations offered in the case of cortical analgesia may hold in certain of these cases too.

Tactile sensibility.—More difficulty is encountered in dealing with the disturbances of tactile sensibility arising from cortical lesions, partly owing to the variability in the responses of the patient to different forms of stimuli, and partly to the fact that another, a psychical, factor has a large influence on the results obtained by delicate tests at least.

In order to understand the alterations in touch produced by cortical disease, we must first study the reaction of the patient to graduated and measurable stimuli, as von Frey's hairs or any reliable æsthesiometer. It was mainly on these measurable tests that Head and Holmes relied in their investigations. When von Frey's hairs are used the patient's responses are irregular, no matter what strength of hair is employed as long as it does not produce pain or discomfort. The patient may, for instance, appreciate a certain number of contacts with the weakest

hair that can be felt on the normal side; and yet contacts by a much stronger hair do not evoke a greater proportion of correct replies. It is, in other words, impossible to obtain a threshold below which no contacts are appreciated and above which all are perceived. Head's explanation of this phenomenon is that, as a result of the cortical lesion there is a defect in local attention, and it is difficult to see what other adequate explanation of it can be offered. This hypothesis also explains other phenomena that result from lesions of the cerebral cortex.

This does not mean that there is a general diminution of the faculty of attention, as Marie and Bouttier assume. They are, of course, correct in pointing out that the reliability of every subject varies from day to day under the influence of external agents as well as of intrinsic causes, but here we have a condition quite different from that associated with disease of the sensory cortex, for in a patient with a unilateral cortical lesion a similar series of tests on normal parts never reveals the same irregularity of response as that characteristic of the affected side. The defect is an immediate consequence of the cortical disturbance, and is therefore limited to those faculties and that portion of the body which are represented at the site of the lesion. Fatigue, inducing a tendency of the patient to fail to respond regularly to a long series of stimuli above threshold value, is evidently closely related to this failure of local attention.

Another common phenomenon is a tendency to hallucinations of touch; if a series of contacts is interrupted the patient may continue to respond at regular or irregular intervals, despite the absence of peripheral stimulation. This curious tendency can be more easily understood when we remember that a contact may be perceived by the agency of the thalamus alone. It is well known that in the thalamic syndrome sensations evoked by peripheral stimulation may outlast the stimulus for a longer period than is normally the case. One possible explanation of this persistence of sensation is that the anatomical lesion damages the paths by which the cortex under normal conditions inhibits or "puts a brake upon" thalamic activity, a function that is obviously necessary for discriminative reaction to environment. A superficial injury of the brain may similarly release, though in less degree, the thalamus from cortical control and thus permit a perseveration of sensations evoked at its level.

In stationary cortical lesions a complete insensibility to contacts with cotton-wool, a camel's hair brush and other tests in common

clinical use is never found, although on hairless parts particularly the patient's responses are irregular and a stronger degree of pressure may be necessary to elicit regular responses. I am aware that this statement is at variance with many of the descriptions of cortical hemianæsthesia found in the literature. It is, however, my own experience in all cases where the lesion is limited to the cortex and the immediately subcortical white matter, though a definite raising of the threshold is often met with when the disease extends deeply into the white matter. Head has also described it in association with subcortical and capsular lesions.

The reason of this discrepancy is probably to be sought in the nature of the clinical material investigated; in some cases the lesions probably lay deeper than the authors assumed, or in others more than one lesion may have existed.

In dealing with cutaneous stimuli attention is generally directed to their quality and intensity only, but the bulk or size of the stimulus may have a considerable influence on the results of various tests. Under normal conditions, and when there is a definite raising of the threshold, as with spinal lesions, sensations of equal distinctness may be evoked by heavy contacts with a small object, by light touches with a larger test object, and by a light moving contact, but the responses of the patient to these different stimuli may diverge widely when the sensory cortex is injured. The slightest changes can be most easily demonstrated by the use of test objects of small size which are not moved over the skin, as von Frey hairs, and it is these that should be employed when we wish to determine the presence or absence of a threshold. In clinical work, however, stimulating objects of greater bulk, as a wisp of cotton-wool or a camel's hair brush, are generally used, and with these it is more difficult to demonstrate those disturbances of tactile sensibility which Head regards as characteristic of cortical disease. This is particularly so when a moving stimulus is employed, which suggests that the stimulation in succession of separate areas of skin excites and holds the attention more readily than a stationary stimulus. Many of our usual clinical tests are, in fact, ill-adapted to demonstrate the more minute alterations of sensibility that result from cortical lesions.

Postural sensation.—Only a short reference is here required to alterations by cortical disease in those forms of sensation dependent on the deep afferents, for it is universally admitted that the recognition of the position of the limbs in space, the appreciation of movement and the recognition of its direction and range, as well as the discrimination

of weights, are those forms of sensation which are most commonly and most severely affected by lesions of the cerebral cortex. Head has dealt with this question very fully, and I have nothing new to add to his observations. In this discussion we are concerned with the symptoms produced by cortical disease, and scarcely with the physiological and psychological problems they raise. It is, however, necessary to insist that the sense of position and movement may be intact, though other sensory functions, as the response to graduated tactile stimuli and the discrimination of compass points, are affected.

In ordinary clinical work the measurement of the angle of movement necessary for the recognition of its range and direction is rarely necessary, as a series of simpler tests usually reveals the degree of the defect.

Vibration.—The tuning-fork is one of the least useful tests in cortical disease, for, as Head has shown, the appreciation of vibration is possible through the thalamus alone, and there is usually at the most only a subjective difference between parts where a disturbance of cortical sensibility exists and the corresponding normal parts. Head, however, emphasizes the fact that vibration and passive movements are usually abolished together; Marie and Bouttier dispute this, and my own experience is that the appreciation of vibration may be little altered though there be considerable loss of the sense of position and of movement.

"*Astereognosis.*"—The commonly used term "stereognosis" has been applied indiscriminately to the ability to identify familiar objects by handling them, and to the power of recognizing the similarity or difference in form of objects placed successively in the hand. There is, however, an essential difference between these two faculties. In the one test we merely examine the patient's ability to recognize similarity or difference; in the other we require of him to name an object familiar to him by other sensory attributes, such as its visual and other characteristics. The first is a function of the sensory cortex, the second a more complicated associational process, to the disturbance of which Wernicke applied the term "asymbolia," and others "tactile agnosia." We may, in fact, find as a result of cortical lesions both an inability to recognize the tri-dimensional form of an object, and an incapacity to identify it with an object already known, even though its form is recognized. In dealing with sensory disturbances of cortical origin, it is the power of recognizing similarity or difference that should be tested, though the power of identifying the object is also a valuable sign.

There has been much discussion on the nature of so-called "astereo-

gnosis." *A priori* one might assume that a patient would be unable to recognize the shape of an object by handling if he were unaware of the spatial relations of his fingers while passing over it, or if tactile localization were defective. It has, in fact, been attributed both to a loss of the appreciation of position and movement, and to defective power of localization. Campora [1] has recently claimed that it results only from a disturbance of tactile discrimination, as revealed by Weber's test. Head has, however, shown that the recognition of form may be unaffected though the appreciation of movement is lost, and that though tactile discrimination and recognition of form are frequently lost together, this is by no means always the case. Appreciation of form can therefore not be correlated with defects in simpler forms of sensation; it is a special and fundamental property of the cortex, dependent upon physiological impulses integrated at a lower level of the nervous system.

Localization.—Disturbance of tactile localization also frequently results from injury of the sensory cortex, and it is frequently a valuable sign in the diagnosis of cerebral lesions.

The most satisfactory method of testing localization is the modification of the Henri method introduced by Head and Holmes, as in it the task set to the patient is as simple as it can be. There are many sources of error in merely asking the patient to indicate with his finger the point touched, for if he has not an accurate knowledge of the position the limb occupies in space, he will be obviously unable to find the point, even though tactile localization is undisturbed. The tendency to refer the stimulus to one direction, as proximally or distally, is due chiefly to the employment of this method. When the Henri method is employed no constant reference in any one direction is found when the cortex only is involved: the patient has simply defective appreciation of localization and his replies are only guesses or approximations.

Compasses.—Weber's compasses are not so regularly employed in clinical work as they deserve to be, for disturbance of the discrimination of one and of two simultaneous contacts is frequently the most striking effect of a lesion of the cortical sensory zone. It is not, of course, a test of tactile sensibility only, for Head and I have shown how the power of distinguishing one and two simultaneous contacts may be lost though tactile sensibility is unaffected to threshold and other tests. It is true, however, that a rise of tactile threshold is usually accompanied by some disturbance of two-point recognition. Head has pointed out that when the response to tactile stimuli is incon-

stant the patient may call two contacts "one," or one contact "two," with equal frequency; but that if there is a specific loss of discrimination the tendency is to call both single and double contacts "one."

I have frequently found the compass test a most valuable sign in the localization of cortical lesions. In two cases of endothelioma growing from the falx and compressing the mesial aspect of the hemisphere some distance behind the fissure of Rolando, and in a case of glioma of the cortex and subcortical white matter of the same region, which were recently under my care, a disturbance of the compass test was the only localizing sign.

One of the three cases was a woman, aged 34, who for five years complained of headache, occasional vomiting, insomnia, and at rare intervals spasms of her right foot. She came under observation with bilateral papilloedema and failing vision. An operation was urgent owing to the danger of blindness ensuing, but there were no motor or reflex changes, no restriction of her visual fields, no affection of the functions of her cranial nerves, and no sensory loss except to the compass test on her right foot. On the dorsum of the left foot she was always correct when the points were separated by 3 cm., but on the right foot she frequently failed to recognize them, even when they were 5 cm. apart. On the inner aspect of the left sole the threshold was 3·5 cm., but a threshold could not be obtained with the points separated to even 10 cm. on the right side. In this case there was no defect of the sense of position or of movement, nor disturbance of any other form of sensation.

All these forms of sensation in which the cortex is directly concerned may be lost together or separately. The generally recognized rule is that in pure cortical lesions those forms subserved by the deep afferents, and consequently those which give us information as to the position in space of parts of our body, the spatial relations of different portions of our limbs and of their movement, as well as the power of recognizing the shape of objects by handling them and their weight, are more affected than cutaneous sensibility.

Head distinguishes three main functions of the sensory cortex: (1) The appreciation of relationships in space; (2) the faculty of reacting appropriately to stimuli of different intensity; and (3) the recognition of similarity and difference of test objects of various weights and shapes. He recognized that these three functions are not always affected uniformly or equally, and consequently concluded that they are not equally represented in all parts of the sensory cortex. There can be no doubt that we frequently find the sensory functions included in each of these groups affected together, but from such cases

as that quoted above, in which compass discrimination only was disturbed, it is obvious that a further dissociation of these groups is possible. It is, indeed, probable that most of the elementary functions of the sensory cortex may be affected separately, but this is rare. The recognition of posture, the distinction of form, and the discrimination of compass points are undoubtedly those elements in which disturbance can be most frequently observed and most easily demonstrated. Defective recognition of differences in weight is another delicate sign that often reveals slight affections of the cortex, but it is not so easily employed in clinical work. On looking through a long series of cases investigated by Head and myself, I find that in every patient but one in whom any disturbance of sensation was present, there was a defect in the weight test. Next in order came a disturbance of the appreciation of position and of movement, and of the compass test.

There is a tendency in clinical medicine to establish "syndromes," or groups of separate symptoms all of which suffer or escape together in disease, but it does not seem that any useful purpose can at present be served by the definition of such syndromes referable to the sensory cortex. Further investigations may show that lesions of separate portions of the cortex may affect constantly certain forms of sensation and these only; but at present it is wiser to recognize the many different sensory faculties which may be disturbed by cortical disease, and to treat each as a separate unit.

Distribution of Sensory Disturbance of Cortical Origin.

The disturbances of sensation produced by a lesion of the sensory area of one hemisphere are always limited to the opposite side of the body. It is true that certain authors have described bilateral sensory loss from unilateral cortical disease, especially of the left hemisphere, and that the investigations of Dusser de Barenne have led him to the conclusion that the sensation of both sides of the body is represented, though in different degree, in each hemisphere; but there is no convincing evidence that in man bilateral disturbance ever results from a unilateral lesion of the sensory area.

The sensory loss may extend over the whole of one side of the body, or it may be limited to a limb or a portion of a limb. When the loss is of hemiplegic distribution the limbs are almost invariably more affected than the face or trunk. This is due partly to the fact that in the limbs loss of spatial perception is usually the most prominent feature, while

the face and trunk are but poorly endowed with sensibility of this quality. It is true that the compass test, and tests for localization and the distinction of differences in weight can be applied to the trunk, but here the thresholds for compass discrimination and weight are so high and so variable that it is not always easy to be certain of the existence of changes of pathological significance. Cutaneous localization is also more vague and much less accurate on the trunk than on the limbs.

The sensory disturbances are usually more marked in the distal than in the proximal segments of the limbs, probably owing to the higher and more complex sensory functions of our hands and feet than those of our arms and thighs, and to their wider representation in the cortex.

A segmental loss is frequently described, that is, an anæsthesia of some form limited to a hand or a foot, or an arm, or a leg, but in cortical disease there is never a sharp or definite limit to the sensory defect; when tactile sensibility or the appreciation of differences in temperature, for instance, is disturbed, the loss fades away gradually into the region of normal sensibility, and spatial disturbances of severe degree in one segment are usually associated with similar, but perhaps less, change in the adjoining segment.

It frequently happens that the disturbance of sensation is apparently limited to, or at least more pronounced on, one side of a limb, as on the radial or ulnar border of the hand, or on the inner or outer aspect of the leg. Anæsthesiæ of such distribution have been variously interpreted. Russel and Horsley [14] assumed a re-representation in the cortex of the type of sensory localization that exists in the spinal cord, and in addition a special representation in the brain of the pre-axial and post-axial sides of the limbs. Others, as Goldstein [4], Krüger [8], and Marie and Bouttier, describe anæsthesia of radicular areas, while Goldstein assumes the existence of special cortical mechanisms concerned with functionally related parts of the body to explain some of the phenomena he has observed.

I have frequently investigated cases in which disturbances of sensation appeared to be limited to, or were more pronounced on the ulnar or the radial side of the hand, or on the inner or the outer aspect of the foot, but in such cases there is never a sharp division between the anæsthetic or the normal parts, nor do the borders of the anæsthesia ever correspond with, or even approximate to, the lines that separate contiguous root areas.

Head [6] has shown that when there is in the little finger a severe

loss of any form of sensation, the same loss is present, though perhaps less pronounced, in the fourth finger, and to a still less degree in the third. In other words, the defect in each form of sensation diminishes gradually from the most affected part towards normal parts. He has also demonstrated that when, as a result of a small cerebral lesion, there is a general loss of cortical sensation in the little finger or thumb, certain functions may be lost in these parts only, others are disturbed in the neighbouring digit too, while some functions may be affected over the whole hand. If, for instance, there chance to be a tactile disturbance on an area that approximates to the cutaneous distribution of the ulnar nerve or of the first thoracic root, there will almost certainly be a postural defect or a diminution of compass discrimination, or of the appreciation of weights, in other digits. A complete investigation of these so-called "radicular" or "axial" anæsthesiæ in fact usually shows that the loss of sensation as a whole, or the disturbance of each separate sensory function, diminishes gradually from the part most affected towards normal parts. There is rarely a definite line between the normal and the anæsthetic areas, and never a line that corresponds to the borders of a spinal root area, or to an axial topography. The terms "axial" and "radicular" anæsthesia are incorrect and misleading when applied to sensory disturbances of cortical origin.

Numerous observations, however, point to a topographical representation of the fingers in the sensory cortex, in a manner similar to their motor representation in the precentral gyrus, and this can explain the local anæsthesiæ often observed in the hands. As the most circumscribed lesions of the motor area never produce a paresis limited to one finger, it could scarcely be expected, in view of the more complex functions and organization of the sensory cortex, that a lesion of it would produce such a strictly limited sensory loss.

In one interesting type of cortical sensory loss which has been observed by Head, Goldstein and others, the face, and more particularly the angle of the mouth, is affected at the same time as the radial portion of the hand. Niessl von Mayendorf [13] suggests that this may be explained by the cortical arterial distribution, as a branch from the middle cerebral artery, which he names the arteria inter-opercularis parietalis, provides the blood-supply to the lower third of the post-central gyrus, where he assumes the face and the radial side of the hand are represented. When this artery is occluded these parts suffer together; when it escapes, but other arteries supplying the post-central gyrus are thrombosed, the face and the thumb escape, but sensation is

affected on the ulnar border of the hand, on the arm and trunk, and perhaps on the lower limb.

The Sensory Zone of the Cerebral Cortex.

There has been much discussion on the position, and especially the extent, of the cortex that has direct sensory functions. Experiments on animals cannot yield us the exact conclusions furnished by Grünbaum and Sherrington and by the Vogts on the extent of the motor cortex. Observations by Cushing, von Valkenberg and others, on conscious patients have, however, shown that peripherally referred sensations can be excited from the postcentral gyrus.

The question whether the precentral cortex has sensory functions has been a matter of much debate. Most of the older physiologists refused to recognize separate localization of sensory and motor functions, and many clinicians, as Head and Horsley, have insisted that sensation may be disturbed by lesions limited to the precentral gyrus. But there has lately been a tendency to limit the sensory zone to the parietal lobe. My own observations on gunshot wounds and other lesions of the brain have led me to the conclusion that the sensory area lies entirely behind the central fissure, and that the precentral gyrus has no sensory functions.

The posterior limits of the sensory area are less easily defined; it certainly extends over the whole of the postcentral gyrus, over the greater part at least of the superior parietal lobule, and probably on to the anterior part of the supramarginal gyrus.

The conclusions to which Dusser de Barenne [2, 3] has come from the application of strychnine to circumscribed areas of the cortex must be referred to here, though the exact interpretation of his observations is still doubtful. He found that immediately after applying strychnine to a small area of the cortex either in front of or behind the central fissure, various symptoms appeared on corresponding parts of the two sides of the body, which he regarded as manifestations of hyperæsthesia and hyperalgesia due to excitation of cortex with sensory functions. When, for instance, strychnine was applied to the middle of the left postcentral gyrus he obtained an exaggerated reaction to light touch and to painful stimuli on both fore-limbs, but more on the right than on the left. The region of the cortex from which these exaggerated reactions could be obtained extended forwards over the precentral gyrus up to the sulcus arcuatus, and posteriorly to the first temporal sulcus, and he therefore concluded that this is the zone most intimately

associated with sensory functions. When strychnine was applied to the motor area of either the arm, the leg, or the face, the symptoms were found in the arm, leg, or face only, and he therefore concluded that there is a sharp separation between the sensory representation of these parts of the body in the cortex. From his observations he concludes also that both the precentral and the postcentral cortex are concerned in sensory perception, but he regards the postcentral cortex as a projection area, while the precentral brain contains associational and correlating mechanisms.

It seems to me doubtful whether these observations have any direct bearing on the question of sensory localization. There can be no doubt that the reaction of the animal to sensory stimuli may be modified by the application of strychnine over a large zone of the cortex, but this may depend on a lowering of the threshold, or on some other change in the excitability, of those portions of the cortex through which such reactions are normally excited, and not on the action of strychnine on portions of the cortex directly concerned in sensation. We are certainly not yet justified in applying Dusser de Barenne's conclusions to clinical work. This is the more probable as he obtained bilateral symptoms from the unilateral application of strychnine, while it is almost universally admitted that a lesion or an irritation of the one hemisphere produces negative or positive sensory symptoms on the opposite side only.

Both clinical and experimental observations, however, indicate that there is a separate representation of the limbs and segments of the limbs, as well as of the trunk and head, in the sensory cortex, and that this representation corresponds to the focal representation in the motor area. In fact, we have in the postcentral gyrus the head segment, fingers, arm, trunk, leg, and foot, represented in this order from below upwards on the surface of the hemisphere.

It is also probable that special sensory functions are separately represented in the cortex. Several authors, as Mills and Weisenburg [11], for instance, have localized a special centre for the recognition of form in the superior parietal lobule, and others have mapped out in the cortex special zones for cutaneous and deep sensation. Goldstein, for instance, localizes cutaneous sensation in the anterior part of the postcentral gyrus, and the sense of position and movement and stereognosis in the posterior part of the postcentral gyrus and in the supramarginal gyrus. There is, however, no general agreement in any scheme of localization; von Monakow, for instance, assumes that the further forward the lesion is placed the more cutaneous sensation is affected,

while the more posteriorly it lies, the more muscle-sense is disturbed, but Redlich has come to an exactly opposite conclusion. Head [6] admits that his localization of special functions is only tentative, but believes that reactions to spatial tests are disturbed chiefly by lesions far forward in the sensory area and in the precentral cortex; that ability to recognize weights and shapes is affected mainly by lesions of the postcentral gyrus; while the responses to stimuli of graduated intensity, and especially to tactile stimuli, are disturbed by disease of the lower portions of the postcentral and precentral cortex, and of the angular gyrus and of the superior parietal lobule.

We obviously require a large series of cases in which the isolated disturbance of a special sensory function, or of groups of closely related functions, can be correlated with circumscribed and quiescent lesions of the cortex, the limits of which have been verified by adequate anatomical methods. As yet we do not possess such cases in sufficient number to justify a general conclusion. Many observations bearing on this point have been published, but in most of them either the clinical descriptions or the anatomical investigations are incomplete.

My own views are based upon the observation of a large number of cortical lesions, as gunshot wounds, circumscribed tumours seen and removed by operation, and local softenings, in many of which the approximate site of disease, at least, could be determined, as well as many cases in which the exact localization of the lesion could be proved.

Few of my cases are conclusive, but my experiences as a whole lead me to believe that some sensory functions, as the identification of form, the discrimination of compass points, and perhaps the comparison of weights, are more widely represented in the cortex than tactile sensibility or the appreciation of position or movement. The sense of position suffers chiefly when the postcentral gyrus is involved; more complex faculties, as the recognition of form, may be also influenced by lesions of the postcentral gyrus, but are also affected by lesions lying more posteriorly in the parietal lobe; while the altered responses to tactile stimuli, which Head and I have described, and loss of localization, are found chiefly when the lesion lies immediately behind the central fissure.

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(4) DYSÆSTHESIÆ AND THEIR NEURAL CORRELATES.

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The clinician is frequently confronted with cases a prominent feature of which is the occurrence of so-called "subjective" or "spontaneous" sensations of one or other modality. Terminology here is not a little confusing, for all sensations are subjective, being experienced in consciousness by a subject, whether they arise from extrinsic stimulation or not. Further, use of the term "spontaneous" is no less unsatisfactory, since excitation by some form of stimulus, extrinsic or intrinsic, however elusive, trifling or untraceable it be, must be postulated if sensation is to come into existence at all. It has been customary to include under the expressions "paræsthesiæ" or "dysæsthesiæ" such abnormalities of sensation as appear to develop spontaneously, and these may pass muster for the purposes of the present communication, even though their connotation varies considerably. "Paræsthesia," for example, signifies, according to the French school, any disorder of sensibility which cannot be classed either as an "anæsthesia" or a "hyperæsthesia." The latter, however, is as a rule diagnosed only by objective exploration of a given part, as is the existence of "anæsthesia"; and while it is true the patient often enough complains of a sensation of "numbness" or "deadness" in an area shown objectively to be distinguished by loss of the appreciation of cutaneous stimuli, the clinician rarely if ever employs the term "anæsthesia" for this subjective sensory condition. Moreover, objective anæsthesia may be unassociated in consciousness with any subjective phenomenon of the above class.

In view of these and other somewhat conflicting interpretations, it seems to me preferable to utilize the word "dysæsthesiæ" comprehensively to include all such apparently spontaneous disturbances of sensation as our patients describe under the rubrics of "burning," "coldness," "wetness," "numbness," "deadness," "tingling," "pricking," "pins and needles," "pain," "sensation of something moving," etc. There is no end to the catalogue, one might think, especially if we are to incorporate those picturesque attempts on the part of the

hypersensitive neurasthenic to give expression to his cephalic discomfort by such similes as: "I feel as if my brains were being stirred about with a red-hot poker." None the less it will probably be admitted that in respect of the ordinary dysæsthesiæ a classification more or less in accordance with the usual divisions of sensory experience is possible. For this paper I shall not consider (unless incidentally) the complexities of feeling just alluded to, or the subjective disorders of the special senses commonly called hallucinations, but shall confine the discussion to those that arise in connection with organic lesions of the somatic sensory system. A somewhat rough-and-ready grouping may be made as follows:—

(1) Tactile dysæsthesiæ.
(2) Painful dysæsthesiæ.
(3) Thermal dysæsthesiæ.
(4) Complex dysæsthesiæ (e.g., wetness).
(5) Dysæsthesiæ with sensation of movement.

(I) Preliminary Considerations.

Certain preliminary considerations may pertinently be dealt with at this point.

(1) If for a moment the phenomena which here concern us may be thought of as "subjective sensations," in contradistinction to "objective sensations" produced by known objective excitations, the fact remains that they are not to be regarded as differing in any subjective respect from the latter; the experiencer is aware of a sensation of coldness, for instance, entirely comparable to that effected by the application of a cold substance to the skin; only because of the apparent absence of extrinsic stimuli is its description as "subjective" justifiable, since, as we shall see, its objective causation by some abnormal physiological factor can, in many cases at least, be fairly established. In others, however, search for a cause may prove negative, yet we cannot think them actually causeless.

(2) Sensations are psychical things, arising in association with certain physiological processes in the nervous system. In the course of this study evidence will be adduced to prove that dysæsthesiæ appear in consciousness as a result of lesions at differing physiological levels—peripheral, spinal, bulbar, thalamic, cortical; but whatever the physiological level the psychological level is always the same, so to speak; in other words, we must bear in mind that sensations, however variously

derived from the physiological viewpoint, are constituted uniquely by changes in consciousness. Since the term "receptor" is in common use for a sensory end-organ, Parsons [1] has recently suggested that ambiguity would be removed were "reception" and "recept" to be employed psychologically for the act of sensing and the object sensed. It would then be easier to distinguish between sensation and perception, for the latter, the act of perceiving, consists in the integrating of sensations ("recepts"). Even when the sensation is simple it does not constitute the fundamental psychological unit—this is the percept, and there is no such thing as a pure or isolated sensation. When, therefore, we shall have occasion to speak of the "subjective sensations" or dysæsthesiæ of our cases, we cannot stop short at any point as though these existed by themselves; we must consider also the emergence of the sensations in a perceiving consciousness, their possessing affective tones and cognitive accompaniments.

We cannot know the sensations of our patients except by their description of them, which of course is a matter of speech. Elementary as this remark is, it has a distinct bearing on at least one aspect of the problem; for it implies that the way must be open between the sensation-experiencing mechanisms and the cortical speech-mechanism, and this is of significance, as we shall see subsequently, in connection with the subjective abnormalities of the thalamic syndrome.

(3) It follows from the above consideration that dysæsthesiæ exhibit the usual variations in degree, extent, duration, of all sensory experiences; they are modifiable by attention, and by other factors of the psychical series. At the same time, their essential crudeness, relative simplicity and primitiveness must be emphasized. The presentations are of recepts which can be analysed and discriminated one from another, but in a given case as a rule only one form is present at a time, combinations of the painful plus thermal type, or tactile plus thermal type, being on the whole less frequent. As remarked already, in a general sense dysæsthesiæ are considered to be "spontaneous," but clinically we find numerous illustrations of the fact that they are influenced by extrinsic agents, such, for example, as cold or warm currents of air, the contact of substances (e.g., water of differing temperatures) on the parts affected, and so forth. Further, the clinician often observes cases where dysæsthesiæ do not seem to arise in consciousness unless and until some such extrinsic excitation occurs, as when the patient declares, for instance, that the wind blowing on his face awakens such-and-such an unpleasant sensation, or when the causalgic sufferer is in comparative

comfort until an extrinsic stimulus (and it may be of quite another order than the cutaneous sensory kind) arouses unbelievable pain. It would be rather undesirable to exclude such cases from the "spontaneous" category, for the good reason that excitation frequently only accentuates or aggravates an already existing if faint dysæsthesia. On the other hand, there appear to be equally numerous cases in which the subjective sensations remain uninfluenced by extrinsic stimuli and the application of extrinsic agents.

(4) Since we shall be dealing with painful dysæsthesiæ and with so-called spontaneous "central" pains, a brief preliminary excursus on the nature of pain will not be out of place.

In accordance with what has already been remarked, while sensation and perception are distinct processes—considered psychologically—the former cannot occur independently of the latter. No sooner is a sensation felt than the localization of the point stimulated and the interpretation of the particular variety of sensory excitation follow as associative reactions; a cognitive element is inevitably added, and an affective element as well; indeed, the sensation may evoke symbolic representations of another kind (e.g., verbal) and may issue in motor reactions. Perceptive function bridges the gap immediately between the purely sensory and the intellectual. When we speak, as we constantly do, of "sensations of pain," or of the "sense of pain," this consideration must not be lost sight of; testing clinically for pain appreciation, thinking physiologically of pain-spots, pain-fibres, pain-centres, we are apt to overlook the fact of its being something more than a pure sensation. As Piéron [2] says, "une sensation de 'douleur' est aussi en réalité un complexus de sensation et de réaction affective," and the receptive systems concerned therewith only enter into thought as a result of "répercussions affectives." He makes an exception, however, of pricking, holding that the character of the sensation can be fairly well discriminated and isolated from the "répercussion douloureuse," unless this is exaggerated. Some recent writers, e.g., Foerster [3], prefer to speak of a *feeling* of pain and not of a *sensation* of pain (*Schmerzgefühl* as opposed to *Schmerzempfindung*). The association of pain feeling with sensations of another kind is well recognized. Thus a pin-prick awakens a "sensation" of touch-pressure of a point plus a "feeling" of pain; the application of extreme hot or cold stimuli arouses the specific "sensation" plus a "feeling" of pain (*Wärmeschmerz*, *Kälteschmerz*), which by introspection can be felt to come later and to last longer than the hot or cold sensation. Yet under many other conditions, and par-

ticularly in pathological circumstances, pain exists by itself and cannot be considered other than a sensation loaded with a specific affective tone of unpleasantness. This is indubitably the case with the "central pains" of nervous disease and with other varieties of neuralgia. Again, in certain diseased states other sensory systems, those for instance concerned with the appreciation of tactile and thermal excitations, may be incapable of conduction, while painful excitations can still be experienced in consciousness; in cases of pure lesions of the dorsal columns of the cord a stroking touch on the skin can cause unbearable pain—a reaction included by Foerster under the useful term of "hyperpathia," which must be carefully distinguished from hyperalgesia.

From the clinical standpoint, if the above-mentioned amplifications are borne in mind, it remains convenient to speak of sensations of pain and of physiological systems concerned with the conveyance of painful impressions, as well as of cerebral centres or zones the integrity of which is essential for the appreciation of pain in consciousness.

(II) Levels of Lesions associated with Dysæsthesiæ.

(1) *Peripheral Level.*

With lesions involving the sensory protoneurones different forms of dysæsthesia are prone to make their appearance. These are observable perhaps as well after alcoholic injection of the trigeminal nerve or Gasserian ganglion as anywhere else; my first illustrations will be from trigeminal cases.

Case 1.—A. C. M., female, aged 57. Has suffered from left facial neuralgia for three years. In January, 1927, I injected the inferior division (the regional distribution of the pain) at the foramen ovale. There has been no neuralgic paroxysm since, and the corresponding cutaneous area remains anæsthetic. But dysæsthesiæ abound, as the following excerpt from a letter of March 28 reveals: "My face still gives me a lot of trouble. I cannot describe the various feelings in it. Sometimes it is very, very *cold*: then again it will *burn* very much; it is burning a great deal to-night and is almost unbearable. . . . Sometimes my lower lip feels as if it is *swelling* so much that it will burst. . . . Again it seems as though there are threads *pulling* from my temple to various parts of the side of the face."

In this lower division thermal, tactile and painful stimuli are no longer appreciated.

Case 2.—M. A. F., female, aged 58. Has suffered from right trigeminal neuralgia for eight years. Apart from typical neuralgia, mainly in the middle and lower divisions, this patient complains that there is a constant feeling as

though the cheek were *wet*, and she frequently puts her hand up to her face as if to wipe it, but it is quite dry. On the most careful objective examination I could not satisfy myself of any impairment of any form of sensibility. After a gasserectomy the *wet feeling* disappeared.

These two cases have been selected with a view to furnishing a comparison and contrast; in the second the hygric dysæsthesiæ were spontaneous, unassociated with recognizable objective sensory change, and vanished after operation on the ganglion; in the first the thermal and other dysæsthesiæ only occurred after interference by injection, and developed in an area which was objectively anæsthetic, thus approximating to an anæsthesia dolorosa.

Other illustrations of dysæsthesiæ in connection with sensation at the periphery can be taken from experience of *causalgia*, the well-known "burning pain" described originally by Weir Mitchell, Morehouse and Keen [4] in 1864, during the American civil war, in a slender volume devoted to injuries of nerves. From this *locus classicus* a few passages of significance will be quoted.

"It is a form of suffering as yet undescribed,[1] and so frequent and terrible as to demand from us the fullest description."

"We have some doubt as to whether this form of pain ever originates at the moment of the wounding; but we have been so informed as regards two or three cases."

"The seat of burning pain is very various: but it never attacks the trunk, rarely the arm or thigh, and not often the fore-arm or leg. Its favourite site is the foot or hand."

"Its intensity varies from the most trivial burning to a state of torture which can hardly be credited."

"The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperæsthetic."

"Most of the bad cases keep the hand constantly wet, finding relief in the moisture rather than in the coolness of the application."

"It appears quite certain that in cases of glossy skin burning always exists. It is also certain that it may exist without association with diseased skin."

"The temperature of the burning part we have always found to be higher than that . . . of corresponding points on the other half of the body."

"If the burning were a referred sensation, it would sometimes be met with in cases of complete division of nerves, and, therefore, in parts devoid of tactile

[1] For the sake of accuracy in neurological history and because of its value, I think it right to point out that a case of causalgia conforming entirely to the descriptions of half a century later was reported by Alexander Denmark, under the title of "An example of symptoms resembling tic douloureux, produced by a wound in the radial nerve," in the *Medico-Chirurgical Transactions*, December, 1813, vol. iv, p. 48. The case was that of a soldier wounded at the storming of Badajos, April 6, 1812.

sensation. But we have encountered no such cases: and, on the other hand, the burning pain is often accompanied with hyperæsthesia, while motion and touch may remain unaltered."

The important and peculiar features of causalgia may thus be tabulated: (1) It occurs with some lesions of peripheral nerves only, and in some nerves (e.g., the median) more regularly than in others. (2) It does not develop at all if the nerve is quite cut across, and is often at a maximum where physiological discontinuity is minimal. (3) It is aggravated by warm or dry applications, and relieved by wet and to a less extent by cold. (4) It is accompanied by phenomena of a different order from those of pure sensation, viz., local raising of skin temperature (by no means constant), local sweating, local alteration in skin colour (intensification of pinkness or redness of skin, even to purple, sometimes in a rather blotchy way); in other words, phenomena of a vascular and neurosympathetic kind are superadded to those of sensation. A further feature of no little interest is the excitation or accentuation of the pain by stimuli of an emotional kind, and especially by those belonging to other sensory systems—so-called alloparalgia or synæsthesalgia. Of much significance are the vascular and neurosympathetic accompaniments already mentioned, since they point to the conclusion that part at least of this peculiar sensory syndrome is attributable to implication of fibres which do not run entirely with the ordinary nerve-trunk fasciculi. In fact, the question arises whether under certain conditions the appreciation of pain is independent of anatomical paths of the peripheral nervous system proper, and further evidence in this respect will be examined more closely at a later stage.

From a large collection two illustrative examples will be chosen.

Case 3.—*Causalgia of the radial branch of the left musculospiral.*—Private McC. was wounded at Loos on September 25, 1915. A bullet entered the left arm just above the elbow-joint and passed out obliquely in a downward direction. When hit, he immediately felt pain down the left hand and fingers, and in the course of a few weeks this became unbelievably acute. It appeared instantly in paroxysms of burning pain on the most trifling provocation, e.g., when the patient in the next bed turned, when music was played, even when his name was called out by the masseur at the ward door.

Operation showed the sheath of the radial nerve to have sticking into it fragments of metal and of bone. The sheath was freely opened and stripped from the nerve, right up to its junction with the musculo-spiral. A considerable degree of relief followed the operation; the spontaneous causalgia largely disappeared, and emotional stimuli similarly ceased to be algophoric.

Case 4.—*Causalgia of the internal plantar branch of the internal popliteal.*—Private M. was wounded at Loos on September 26, 1915. He was shot

through the right leg just above the knee and immediately felt acute pain on the inner side of the sole of the foot. So convinced was he of a wound there that he sat down and took off his boot and sock, but saw nothing. A few minutes later blood began to ooze through his trousers above the knee. In the course of some weeks the pain, which had never ceased, became truly agonizing. The patient sat in bed holding his foot with his hands, pressing it with wet cloths; light touch and pressure caused intolerable burning pain, but firm pressure rather relieved it. A warm or a dry application was insufferable. He used to pour with sweat all over when the pain was unusually intense. Local phenomena of sweating and altered coloration were always in evidence. The most insignificant stimuli (a cough, a patient passing the bed, a laugh, touches on the opposite leg, a rustling newspaper) produced unbearable torture.

At operation, just below the branch to the outer head of the gastrocnemius, a definite spindle-shaped swelling was found on the internal popliteal, and the minute vessels on its surface were hyperæmic. The sheath was stripped off and the nerve freed; the spindle-like swelling was incised longitudinally in various places and the nerve surrounded by fat.

Immediately after the operation the spontaneous causalgia ceased to some extent, though not entirely; and emotional stimuli failed to exert their previous influence.

Testing for objective changes in sensibility is usually a matter of some difficulty in cases of causalgia, as can be realized best by those who have had occasion to try; generally speaking, tactile, thermal, and painful excitations are appreciated, yet it becomes arduous to separate the sensation from its affective accompaniment, since the intensity of the burning pain submerges other qualities of sensation in consciousness. I have not found more than a hypalgesia or hypæsthesia in most instances, while, of course, many exhibit an actual hyperalgesia and hyperpathia, the threshold to painful stimuli being lowered, and the response being altogether disproportionate to the stimulus.

It is of much significance that the causalgic dysæsthesia is not known to occur in its full form, with vascular and neurosympathetic concomitants, except at the peripheral level; it never develops with lesions of the dorsal roots.

Attention must next be directed to the association of dysæsthesia with other peripheral cases distinguished by the presence of definite symptoms and signs of a *vascular* and *vasomotor* kind. I shall not here do more than mention in passing the large group of acroparæsthesiæ, characterized by the development of painful and other dysæsthesiæ, nearly always in elderly women of a hard-working class, who commonly exhibit indications of commencing arteriopathic change. This is an out-patient type *par excellence*, and one which is very clear-cut clinically.

It has always appeared to me feasible to link the occurrence of the very unpleasant dysæsthesiæ largely at night or in the morning with an insufficient blood-supply to the vasa nervorum, a meiopragia or relative ischæmia following on lowered vascular tone during the night hours in minute vessels which are also degenerating.

Other clinical groups, those of acro-asphyxia, acrodynia, etc., and, more generally, those of the Raynaud and sclerodermia categories, have a similar tendency to exhibit dysæsthesiæ often of a chronic and rather intractable kind. Nor should those which accompany intermittent claudication be omitted in this connection. In all of these examples the interrelation of subjective sensory disorder and altered vascular states is unmistakable. A recent case of a peripheral syndrome of the Raynaud-sclerodermia class has afforded a good chance of demonstrating the close connection of the sensory system with the vascular system.

Case 5.—Miss E. C., aged 37, a patient of Dr. C. W. Somerville, of Bonnyrigg. For no less than twenty years the left hand has been the seat of chronic changes involving all the tissues from skin to bone. Some eighteen months ago the right hand, previously normal, began to exhibit similar alterations, which now are as advanced as in the other. In summer the hands are thin and dead-like; in winter they tend to swell up to some extent. The skin of both is shiny, glossy, often discoloured to a bluish-violet hue, and sometimes additionally disfigured by areas of blister-formation. The ends of the fingers, particularly those of the ulnar side, exhibit a panatrophy, rendering them hard and claw-like. The skin temperature of the hands is much below that of the rest of the arms. At the wrist on both sides the radial pulse is very faintly palpable. The patient complains of *absolutely unbearable pain* in both hands, resembling that of causalgia, in that it is aggravated by sensory stimuli of another order. She prefers to keep them cold, since warmth causes intenser suffering, and to let them depend.

Objective examination reveals extreme hyperæsthesia, also as in many causalgic cases, to touch contacts. Cotton wool is everywhere appreciated, and touches accurately localized. Painful and thermal stimuli are normally appreciated, the former, and hot stimuli, exaggerating the continual pain, while cold applications do not aggravate it.

In view of the general resemblance of the symptomatic picture to that of the causalgia syndrome, I suggested a periarterial sympathectomy on the left side, and this was agreed to. On January 17, 1927, the patient was operated on in Edinburgh by Mr. Quarry Wood.

The *brachial artery* was duly exposed at its upper end in the left arm and *was recognized only with considerable difficulty, as it was extremely small, no thicker than an ordinary match.* Its pulsations were very slight, indeed almost imperceptible. The operator decided that it would be impossible to attempt

stripping the periarterial plexus; instead, following the technique of Sampson Handley, he injected a drop or two of 95 per cent. alcohol into the arterial wall, which immediately turned white over a distance of about a quarter of an inch, or rather more, while pulsation ceased at the wrist, though it returned some hours later. The wound healed by first intention.

Soon after the hand felt warm for the first time, and at intervals since it has been warm for a period of many minutes, but it never keeps warm, always reverting to its previous cold state. The pain was at first distinctly "different," being less intense and much less continuous. When I re-examined the patient, however, on February 11, it was just as agonizing as before, and no objective modification of the results of the original sensory tests could be found.

From this puzzling case certain deductions can, it seems to me, be justifiably drawn. The normal responses (normal, that is, apart from the hyperæsthesia and hyperpathia) indicate complete anatomical integrity and physiological conductivity in the nerves of the arm. Again, the concomitants of trophic changes, skin discoloration, low surface temperature, etc., suggest persistent vasomotor alteration in the form of angiospasm, and with these the remarkable reduction in calibre of the brachial artery must, I think, be associated. It is of considerable neurological interest that the alcoholic injection into the artery sheath "changed" the nature of the pain for the time, and also exercised a modifying if temporary effect on the coldness of the extremity. I take this case to suggest that under certain conditions intense pain may be experienced in a limb, derived not from a morbid process in the peripheral nerves but from changes in the periarterial plexuses of non-medullated nerve-fibres and accompanied, it may be, by vasomotor disorder. Such an origin for the pain seems feasible, though the difficulties in the way of the proposed operation prevented fuller proof of the conjecture, and the case, at present, remains incomplete.

Valuable corroboration of the general contention, however, is afforded by Tinel [5], who in cases of causalgia from wounds of the wrist and fore-arm was able to "constater l'existence de troubles dans tout le domaine du sympathique cervical, avec *rétrécissement et vaso-constriction de toute l'artère humérale, dont le calibre ne dépassait pas 2 ou 3 millimètres et dont les battements étaient à peu près nuls*" (italics mine). Analogous cases have been published by Brüning [6]. The similarity of the vascular and sympathetic condition to that of Case 5 is very impressive.

(2) *Spinal Level.*

The appearance of different dysæsthesiæ in association with organic lesions at the level of the spinal cord is a commonplace of clinical obser-

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vation. Reference can be made in a single sentence to the dysæsthesiæ of such conditions as disseminated sclerosis, subacute combined degeneration, tabes dorsalis, and syringomyelia. In these instances the structural changes implicate either the sensory protoneurones on the proximal side of their spinal ganglionic centres, or the deuteroneurones of the cord itself. Conformably with what is known of the re-arrangement of sensory systems in the cord, greater dissociation, i.e., more definite separation, of one type of dysæsthesia from another is to be expected, and is certainly found in some spinal cases, if by no means in all.

Without alluding to all the varieties encountered at the spinal level, I may illustrate more particularly by selecting painful and thermal types, as well as those of a mixed character.

The occurrence of spontaneous or *central pains* and painful dysæsthesiæ in organic spinal disease is now well recognized. They have been studied by Holmes [7] in cases of gunshot wounds of the cord, and have been noted in an occasional case of disseminated sclerosis, in hæmatomyelia, intramedullary tumours and central gliosis, and in syringomyelia. The mechanism of production of these spinal pains falls to be considered in a later section, but I may here point out that as a rule they are quite different from causalgia, and that, in further contradistinction from peripheral cases, they rarely appear in anæsthetic areas —that is to say, the phenomenon of anæsthesia dolorosa often characterizes peripheral and radicular cases, but seldom purely spinal disease. An important case exhibiting this peculiar combination, however, will be described immediately (see below, Case 9).

Thermal dysæsthesiæ in spinal lesions have engaged my attention for years. Along with the late Dr. P. W. Saunders, I collected a number of such cases, but my material has not been published. An impetus to this research was provided by Hughlings Jackson [8], who, in the last "Neurological Fragment" he wrote (1909), expressed the opinion that in some cases of continual over-coldness (so-called "subjective sensation" of cold) the patient might be found to exhibit inability to appreciate hot substances objectively in precisely the same cutaneous area. I was able to give Jackson a reference to a case with this "double symptomatology" recorded by Sir Charles Bell [9] in his work entitled "The Hand."

Case 6 (Bell).—"A man who had lost this sense [sense of temperature] in his right hand, but retained muscular power, lifted the cover of a pan, which from falling into the fire was burning hot, and deliberately replaced it, without

being conscious of the heat; the effect, however, was that the skin of the palm and fingers was destroyed. The same man had a continual sense of *coldness* in the affected arm, which actual cold did not aggravate, nor heat in any degree assuage."

Absence of further details renders diagnosis somewhat problematical, yet it is distinctly possible the case was one of syringomyelia. A more definite, personally observed, instance of this disease may now be quoted in support of Jackson's speculation.

Case 7.—M. B., male, aged 44. Diagnosis, syringomyelia. The patient complains of a constant feeling of *icy coldness* over the whole of the right arm and over the right side of the trunk from the line of the neck and jaw to below the level of the umbilicus. In this region there is complete loss of appreciation of painful stimuli, and also complete loss of the appreciation of heat in any degree, whereas cold contacts are usually (though admittedly not always) recognized.

Another spinal case, one of tabes dorsalis, illustrates the same double symptomatology.

Case 8.—A. H., male, aged 34. The complaint in this instance is one of continual *icy cold* feelings all over the legs and the perineum. "I feel as if I were sitting on a block of ice." "I feel as if a cold draught were blowing over my legs, just as though I had no clothes on." On objective examination the skin temperature of the parts affected is not materially altered from that of normal areas. Loss to pin-prick is complete in the segmental skin areas corresponding to the spinal division from D 12 to S 5, and, in addition, over the whole of this region there is complete loss of thermal sensibility to hot stimuli, whereas cold stimuli are everywhere appreciated, although the patient declares they are not so cold as over normal cutaneous regions.

Thus I am able to adduce clinical illustrations yielding support to Hughlings Jackson's generalization, but I hasten to point out that other clinical cases do not favour it. The exceptions are of two classes: (1) In some cases a subjective thermal dysæsthesia exists with loss of all thermal appreciation; (2) in others it is present though no objective sensory change can be elicited. As an instance of the former of these two groups the following case may be cited:—

Case 9.—A. C., male, aged 73. The patient complains of: (1) A constant *burning* feeling over the right side of the abdomen, and to a less extent over the whole of the right leg; (2) *numbness* over the whole of that leg; (3) extreme *tenderness* ("like an electric shock") to light touch-contacts over the same areas.

The results of repeated tests may be summarized as follows:—

(1) *Touch.*—Over the right leg and up to the level of D 8 cotton-wool

touches are much "less plain" than on the other limb, and several stimuli are actually missed. Stroking with a wisp of wool often causes a hyperpathic response scarcely to be distinguished from pain.

(2) *Pain.*—From the level of D 10 downwards light jabs with a pin are nowhere felt as sharply as on the left. They are less "pointed"; "not so like a pin." Nevertheless they, especially if somewhat harder, provoke more actual pain than on the other side, "as though the right were more tender." In other words, the response on the right partakes of the nature of hyperpathia.

(3) *Temperature.*—The patient is entirely unable to distinguish directly either heat or cold over the region from D 8 down, i.e., there is complete objective thermal anæsthesia in this area. But indirectly a considerable distinction can be drawn as between the two modalities. Thus, when touched on the right side with a cold tuning-fork or cold hand, he jumps, for cold produces a sensation of extreme painful tenderness. Warm or hot contacts, on the other hand, are felt as touch ("like wool"). Hence he can differentiate between heat and cold by noting that a hot test tube produces a "touch" sensation, and a cold tube a "tender" sensation.

(4) The objective *difference between the skin temperatures* of the right and left abdomen and legs is at once apparent to the hand of the observer, as it is to the patient himself. Repeated examination with a skin thermometer reveals a difference of nearly 2° F. on an average between the two sides, more noticeable on the abdomen than the lower limbs.

(5) Finally, there is a constant *difference between the systolic blood-pressures* in the two legs, amounting to as much as 20 mm. Average readings are as follows: Right leg, 105 to 110 mm.; left leg, 125 to 128 mm.; (right arm, 125 to 130 mm.).

Scrutiny of this instructive case allows some conclusions of considerable importance for our subject. Without here supplying the details of the exhaustive neurological examinations that have been made on it, I may say briefly that the symptoms point to the existence of a vascular lesion in the cord, possibly of the nature of a localized myelomalacia, with its upper limit at the level of the seventh or eighth thoracic segment and occupying mainly, as it seems to me, the dorsal horns over a considerable extent in a downward direction. In favour of this localization is the fact that the "ano-genital flap" (Sherrington) does not escape on the right side, and evidence (both experimental and clinico-pathological) has accumulated to suggest that there is an extrafunicular conduction of pain impulses from this cutaneous area by means of what Foerster [3] calls "a continuum of numerous short chain neurones" in the spinal grey matter of the same side. In this Case 9 the absence of motor symptoms, changes in reflectivity, or sensory alterations on the left side negatives anything like a complete Brown-Séquard lesion. There may be some slight implication of touch paths

passing in by the dorsal horn entry-zone to the dorsal funiculi, but the total thermanæsthesia and the analgesia are in favour of a dorsal horn lesion mainly. The pain over-reaction, or hyperpathia, possibly can be taken to indicate that this dorsal-horn conduction is not completely interrupted (v. *infra*).

Of no less interest and difficulty are the two phenomena of local rise of skin temperature with a subjective sensation of burning, and local reduction of a systolic blood-pressure. To account for these unusual features taxes our knowledge of the central (spinal) representation of the sympathetic mechanisms controlling vascular calibre. It is clear in this case there must be a local vasodilatation with relative hyperæmia segmentally set in action, and the conjecture may be allowed that this is somehow connected with the intermediolateral tract and centres in the lateral horns of grey matter on the right side of the cord. For if this speculation be impermissible we are faced with the problem of two separate lesions for the symptom-complex, viz., one presumably spinal, and one in the sympathetic side-chain of ganglia; the likelihood of this latter view seems extremely remote.

Some may doubtless contend that an easier explanation of the syndrome can be found in the supposition that the lesion is not right spinal but left thalamic; the chief difficulty in this respect remains the same, viz., how to account for the local vasodilatation, reduction of blood-pressure, and rise of temperature. I have never seen these peculiar phenomena in any typical case of the thalamic syndrome.

Be all this as it may, the case is cited in some detail to prove that a "subjective sensation" of a thermal class, a dysæsthesia of *burning*, can exist with complete *loss of all thermal appreciation* objectively, and it therefore does not fall in with Hughlings Jackson's hypothesis already outlined.

The second class of exceptions to Jackson's speculation is furnished by cases in which thermal dysæsthesiæ are unaccompanied by any objective sensory changes, of which the following case is an illustration.

Case 10.—W. A., male, aged 57. For about one year the patient has been aware of a feeling of *intense coldness* all over the lower part of the abdomen, genitalia, buttocks, lower part of the back and upper parts of the thighs. So severe is this *icy coldness* that it quite prevents him from continuing with his work. He wraps up his genitalia in cotton wool and swathes his mid-parts with it, to no avail. The only other symptom is some degree of defective vesical control, especially at night. The patient had venereal disease many years ago.

Minute objective examination of the regions affected fails to elicit any

change in thermal appreciation, which is everywhere normal (both modes), or any change in painful or tactile sensibility. The sole alteration is a definite diminution of the sense of vibration in both lower extremities. Reflectivity is unaltered. A Wassermann test in the blood gives a positive reaction.

Although the cutaneous area of the cold dysæsthesia does not, perhaps, conform with rigorousness to a segmental distribution, seeing that while it involves lower sacral zones it omits lower but affects upper lumbar regions, nevertheless certain little signs point to an organic basis for the affection, and the absence of objective thermal change is again, therefore, not in accordance with Jackson's views.

As a final variety of spinal dysæsthesiæ I shall refer to the complex feeling of *wetness*.

Case 11.—C. M., male, aged 43. Diagnosis, disseminated sclerosis.

For a number of years the patient has complained of a persistent *sensation of wetness* in the legs; it is exactly like *trickles of water* passing down the backs of the legs to the heels. So realistic is this feeling that over and over again, convinced of the wetness of the skin of his calves, he has rubbed it with his hand, only to find it normally dry.

Objective examination, repeatedly conducted, has failed to discover any change in any form of cutaneous or deep sensibility in the parts involved, with the single exception that tactile contacts are not invariably appreciated with normal acuity over the areas where the dysæsthesia is localized.

In this clinical instance, it is true, the element of "warm" or "cold" is not added to the "wetness," as often occurs in other cases, yet the sensation passes beyond one of mere formication, of "something moving," since the "wet" component definitely enters therein. The usual symptoms and signs of disseminated sclerosis of a mixed cerebrospinal class are characteristically present.

(3) *Bulbar Level.*

At the levels of the medulla, pons, mesencephalon and regio subthalamica organic lesions implicating sensory paths very commonly are accompanied by one or other kind of dysæsthesia; every variety is known and has often been recorded. In view of the anatomical dissociation of afferent fibre-groups in the fillets corresponding to the forms of sensory experience (as also at spinal levels, already mentioned), the clinician will frequently find the dysæsthesiæ to be peculiarly distinct and uncomplicated. Lesions of the posterior inferior cerebellar artery, as is well recognized, are especially calculated to offer the combination of "subjective sensations" with objective sensory change,

seeing that they involve the formatio reticularis with its ascending spinothalamic paths, as well as the descending root of the fifth and the issuing quintothalamic tracts. Anywhere in the brain-stem below the actual thalamic level spontaneous pains and dysæsthesiæ of the usual kinds can arise as a sequel to structural disease, and choice of material is almost embarrassing.

My present clinical assistant and former house physician, Dr. W. G. Wyllie [10], has studied with minute care a case of syringobulbia, that of a young girl who has been a patient of mine for some years at the National Hospital. In this case one of the earliest symptoms was a sensation of *intense coldness* over the right arm and leg and right half of the body, with similar coldness on the left side of the face. To the dysæsthesiæ there corresponded objectively complete loss of recognition of cold stimuli, which were either said to be neutral or misappreciated as warm. The loss to warm or hot stimuli was much less in evidence; it was no more than partial, for the impulses from very hot contacts reached the sensorium and were correctly recognized, though merely as "warm." In this respect, therefore, Jackson's hypothesis was to some extent confirmed.

Again, two of my former assistants, Drs. D. R. Gowler and B. M. Hope [11], have published the case of a patient of mine at King's College Hospital, which is one of occlusion of the right posterior inferior cerebellar artery. In this instance the patient complained of an *intense burning pain* over the whole of the left side of the body and left limbs, and on both sides of the face, with severe "pins and needles" or painful tingling in the same distributions. Objectively, heat stimuli (about 45° C.) were recognized everywhere, on both sides of the body and face, whereas cold (about 7° C.) were completely missed on the left half of the body (except in the left neck region), and left limbs. There was, on the other hand, no impairment of the appreciation of cold on the right side of the face. Thus (1) the burning dysæsthesia of the left body and limbs co-existed with objective loss of sensibility to cold in the same areas and with conservation of sensibility to heat (for Hughlings Jackson's view); but (2) it occurred over the face on both sides where no loss of either form of thermal experience could be found (against Hughlings Jackson's view).

A number of years ago I [12] reported at length a striking example of the same lesion in which loss of appreciation of all degrees of cold over the right side of the body, right limbs, and both sides of the face was associated with "hot pins and needles," with "tingling warmth"

over the same side of the body and same limbs, yet only on the left half of the face, whereas all degrees of heat were stated (for the right limbs, body and face) to be "tepid" or "slightly warm," and on the left face they were unrecognized. This case, therefore, illustrates the same peculiar correspondence and non-correspondence, at one and the same time, of subjective thermal sensation and objective thermal loss, as does that of Gowler and Hope.

But it is valuable from another point of view. I quote from the original description:—

Case 12.—"Mr. M. had often noticed that *pricking of the left face*, in addition to its being felt as pressure merely, *never resulted in any bleeding*. He had frequently experimented with himself in this connection, and says the same thing is true of the right side of the body. About three weeks ago, however, coincident with the diminution of the 'subjective sensations' on the left face, he found that pricking was followed by bleeding for the first time since the onset of the disease. I re-examined him from this point of view, and can vouch for the fact that blood is much more readily obtained by pricking on the left hand than on the right, whereas there is no difference now between the two sides of the face. There has never been any appreciable difference between the surface temperatures of the two sides of the body."

That some change of a sympathetic or vasomotor nature had occurred over the left face and right body and limbs seems absolutely certain—presumably a degree of general vasoconstriction. The interest of this phenomenon—in association here with complete analgesia—in an organic case is enhanced when we remember the frequency with which it has been observed in hysteria. Further (to quote again):—

"The return of a certain vasodilatation, as indicated by bleeding after pricks on the left face . . . . coincides with a diminution of the 'subjective sensations' of tingling when the skin of the left face is rubbed, and suggests that there may be some connection between the two, especially as these sensations remain undiminished over the right limbs, and here pin-pricks are not followed by bleeding."

I am not aware that other recorded examples of occlusion of the posterior inferior cerebellar artery, or of other organic lesions in medulla, pons, or mesencephalon, have been specially studied from this particular standpoint, but my case does undoubtedly provide material in support of what has already been suggested in this communication, that there is a definite interrelation in some cases between spontaneous dysæsthesiæ and vascular (vasomotor, neurosympathetic) disorder.

Finally, in respect of the brain-stem level, pleasure has been afforded

me by the discovery of a striking instance of a lesion of the posterior inferior cerebellar artery, recorded more than one hundred years ago by Alexander Marcet, M.D. [13], in the second volume of the *Medico-Chirurgical Transactions*, 1811, under the heading "History of a singular nervous or paralytic affection, attended with anomalous morbid sensations."

Case 13 (Marcet).—The case is that of Dr. Vieusseux, aged 62, who had an ictus on January 4, 1808. Thereafter, he was found to show complete analgesia of the right limbs and right side of the body up to the neck, and the left half of the head was also analgesic. Further, thermal appreciation was gravely disordered, as can be gathered from the following excerpts which I have selected.

"An attendant brought him an etherized julep, which he took with his right hand, and the bottle felt lukewarm; but on taking hold of it with the left hand he found it cold, as it really was."

"On putting his right hand into boiling water it appeared so far from hot that he could have kept it immersed without being sensible of its scalding him, had not a disagreeable sensation, different from that of burning, at length warned him to withdraw it." "In plunging into very cold water, the water appeared almost warm to his right side, but very cold to the other."

"There was constantly a *sense of heat* throughout that (right) side, often as if by puffs, or as if hot cloths were suddenly applied to the parts."

"He often had a *sensation of cold water* all over his face, especially when in the open air, which induced him to wipe himself as if he had been wet."

I need not cite further from this century-old case the many graphic details furnished by the self-observation of one of our own profession, and recorded by another with minute accuracy; their work lives after them, and enables us three generations later to recognize the unmistakable symptoms and signs (not all now given) of a lesion of the left posterior inferior cerebellar artery. We here meet with: (1) A thermal dysæsthesia of warmth or heat on the right side, with absolute loss of the opposite mode (cold) on the same side, and with loss also of appreciation of heat. Yet one should note that these two thermal losses were not identical in all respects; "on putting him into a cold bed, it appeared hot to the right side, and cold to the left. In getting into a hot bath, it felt hot to the left side, and neither hot nor cold to the right." That is to say, on the affected side cold things felt hot, but hot things did not feel cold. This distinction, existing with the positive, subjective sensation of warmth or heat, is precisely identical with what obtains in my Case 9 (above), as the following remarks of my patient, given verbatim from the case record, show: "If I get into a

cold bath the water would feel cold to the left leg and hot to the right; if I lie in a hot bath the water feels hot to my left leg, but I do not feel the water at all with my right leg." To the possible meaning of this interesting interrelation for the problem of the physiology of dysæsthesiæ reference is made at a later stage. (2) Marcet's patient also exhibited the phenomenon of subjective wetness on both sides of the face, but from the record it does not appear that this can be linked to any definite, objective, sensory change on both sides; apparently the right face was normal, while on the left side, in addition to the analgesia already mentioned, there was "insensibility to ice." Touch, seemingly, was everywhere intact.

(4) *Thalamic Level.*

"Subjective sensations" constitute an integral part of the familiar thalamic syndrome, the establishment of which we owe largely to the successive work of Dejerine [14], Roussy [15], and Head and Holmes [16]. Whether they assume the form of spontaneous pains and painful paræsthesiæ, or of thermal or tactile or "mixed" dysæsthesiæ, they differ in no material respect from those met with at all the lower levels. Both the hyperalgesia and the hyperpathia which we have seen may result from lesions below the thalamus can similarly characterize affections of the latter ganglion. None the less, thalamic lesions of the class producing the thalamic syndrome proper can be recognized by the occurrence of clinical details which, as they are dealt with by another contributor to this discussion, need not here be particularized.

In view of the confluence of the fillet sensory systems on the thalamus and their ending in its lower (ventrolateral) aspect, a degree of "mixture" of spontaneous sensations is naturally to be expected at this stage. True, the unbearable pains of the typical syndrome usually predominate, drowning other sensory elements in consciousness by their sheer intensity, yet in one or other case some other variety may either co-exist or actually be more pronounced. With these subjective combinations objective variations, ranging from hyperalgesia to analgesia and with corresponding extremes in other sensory divisions, can be observed. For present purposes one or two examples of the syndrome exemplifying rather other dysæsthesiæ than that of pain alone will be chosen.

Case 14.—A. P., male, aged 52. Diagnosis, lesion of right optic thalamus; thalamic syndrome.

The patient had a stroke eighteen months ago, causing a mild left hemiparesis and a much more evident sensory hemiplegia. He complains

of insufferable "*pins and needles*" all over the left side; "I feel as if I were treading on tin-tacks." At one time there is a pricking, *burning* sensation in the left face, trunk and limbs; at another it is *icy cold*. Objectively, the characteristic hyperpathic response of an explosive nature is obtained, more especially with pin stimuli; cotton-wool touch is diminished; cold excitations fail to reach the sensorium, while heat or warmth is much better appreciated. There is no astereognosis, loss of muscular sense, or defect of localization, but the phenomenon of radiation is pronounced. In respect of pain, the "all-or-none" nature of the response prevails: a single mild pin-prick becomes a "stab," and is felt "as if the pin were being dragged deeply along." If not a "stab," it is never felt at all.

This case illustrates painful, thermal, and tactile dysæsthesiæ in one subject.

Case 15.—A. R., female, aged 53. Diagnosis, thalamic syndrome with athetoid movements.

Eighteen months before coming under observation at the National Hospital, now seven years ago, the patient had a stroke (embolic) involving the right side and was unconscious for three days. Multiplicity and inconstancy of duration and degree have been the salient features of the dysæsthesiæ. Thus:—

(1) *Numbness* and "deadness" of the right face, trunk, and limbs is often remarked.

(2) *Tingling* and *pricking* also, but not pronounced.

(3) More persistent is a *burning* feeling all down that side, "something cruel"; on one occasion it was so extreme she actually "thought the bed was on fire," and looked to see.

(4) Again, this is replaced by a *cold* sensation over the right face and limbs, especially the upper, but not the trunk: "just like *pouring cold water* down over the face, neck and arm"; hence a feeling of "rushing" or "moving" goes with it.

The right arm and hand are the seat of unceasing athetoid movements, and the plantar response is extensor.

Objectively, tactile and painful sensibilities are both reduced, thermal (both forms) also, but heat less than cold. Hyperpathia for painful stimuli is much in evidence, and "burning" usually goes with it.

Case 15 similarly exemplifies well the complexity and multiplicity of the "subjective sensations" associated with some organic lesions at the level of the optic thalamus. Other cases of the thalamic syndrome exhibit the phenomenon of alloparalgia already alluded to under the section dealing with causalgia. Some examination of the hypotheses advanced to account for the nature of the dysæsthesiæ associated with thalamic disease can be made more conveniently after our résumé of the data of all the sensory levels is completed.

(5) *Cortical Level.*

Leaving aside, therefore, for the moment, the vexed question of whether the optic thalamus is a terminus *ad quem* for at least one form of sensory experience, viz., that of pain, we must ascertain whether with known cortical lesions paræsthesiæ or dysæsthesiæ can occur, and if so, of what qualities. We are here dealing, be it remembered, with the relatively crude and simple and separable varieties of mere sensation with which an affective element of pleasantness or unpleasantness is inextricably combined, and are not concerned with those definitely higher, more complicated, perceptions which all believe are of cortical site, physiologically speaking, and which in reality partake of the nature of discriminative judgments, e.g., stereognosis and other sensory syntheses, in Parson's [1] terminology, "highly apocritized perceptions." Is there satisfactory clinical evidence of the origination of dysæsthesiæ of tactile, painful, thermal, or "mixed" type from lesions in which only the cortex is involved?

Notwithstanding a vast deal of research, clinical and experimental, no finality has been attained as yet in respect of anatomical cortical areas, responsible physiologically for the appreciation of simple modalities of sensation in consciousness. I shall not here, accordingly, discuss the evidence for and against a precentral, retrocentral, parietal, etc., localization of the sensory projection-systems to the cortex from the thalamus, but simply assume, for clinical purposes, the existence of some degree of separate representation, in the cortex, of the mechanisms underlying conscious appreciation of the ordinary varieties of sensory experience.

Evidence of the occurrence of both subjective and objective alteration in sensation accompanying lesions of cortical site has accumulated over many years, and has been of late excellently recapitulated by Piéron [2] and by Foerster [3], to whose books the student of the subject is referred. The experimental evidence of Cushing [17], derived from operation cases in which the cortex has been stimulated in the conscious state, and of others who have made similar investigations; the animal experiments of Dusser de Barenne [18] and of Minkowski [19]; the material derived from cases of gunshot wounds in war; and, not least, that obtained by patient correlation of clinical symptoms with pathological findings (tumours, vascular disease), all combine to establish the fact that varieties of common sensation can arise from cortical excitation or irritation, and be lost from cortical destructive lesions. Of the genuineness of this conclusion the clinician

has long been convinced. It appears that the representations in the cortex of varieties of sensibility are distinctly unequal, some being more perfect than others. Both of the above-mentioned authorities quote researches of their own, and numerous other published reports, which go to show that pain has a definite representation in the human cortex, as well as thermal sensibility, and that previous conclusions in the opposite sense must be reconsidered. Piéron, for instance, has worked out ingeniously in statistical form the frequency and intensity of injuries (in cortical war cases) to the simple forms of sensibility and elementary modes of perception. Attributing to each sensation a co-efficient running from one (considered normal) to five (complete disappearance), he finds that heat and cold are least affected (3·21), and pain comes next (3·35). Tactile discrimination (3·80), position (4·00), and stereognosis (4·13) are most affected.

The clinician can furnish collateral evidence, as far as the dysæsthesiæ are concerned, derived from the study of cases of Jacksonian epilepsy. Cases of this category in which paræsthesiæ in a limb or limb-segment usher in the epileptiform attack, commonly of the nature of tingling, or of something "drawing" or "moving," are very frequent. I have not, to the best of my recollection, noted a case of sensory aura amounting to *pain*, but tingling or "pins and needles" is not far removed therefrom, while Foerster has observed a case of Jacksonian epilepsy the aura of which was invariably pains in bladder and rectum, followed by paræsthesiæ on one side, and he allows definitely the occurrence of such subjective pain of cortical origin. The following case, also of Jacksonian epilepsy, illustrates well the definite development of *thermal* dysæsthesiæ as a cortical aura.

Case 16.—V. F., female, aged 39. Diagnosis: right parietal cerebral tumour (successfully removed).

This patient suffered from repeated Jacksonian attacks involving the left limbs, beginning in the left hand and spreading quickly to the whole of the left side. *The aura was a "subjective sensation" of icy coldness down the whole of the left side* (face, trunk, limbs), which appeared suddenly a minute or two before the motor symptoms, and remained till they developed, passing off with their appearance. In addition, frequent pains were complained of in the left limbs (not as an aura, but apart from the attack). Objectively, the left hand exhibited astereognosis and loss of muscular sense; touch was lost over the major part of the left side, and pin-prick stimuli were diminished (not lost) distally in arm and leg.

Because of its historical and intrinsic interest reference may at this point be made to the case of Sir Philip Broke, quoted by Weir

Mitchell [20] under the heading, "Subjective false sensations of cold."

Case 17 (from Weir Mitchell).—Sir Philip Broke fell from his horse on August 8, 1820, was concussed, if not completely unconscious, and suffered from confusion, amnesia, and vomiting. "The first symptoms that I remember of any affection of the nerves were my perceiving, in the afternoon of the day following the accident, a sense of *extreme cold* in my leg and foot and left hand, so that I could not sleep in comfort without a worsted glove and worsted stocking; and in the course of the next day I discovered that the whole of the left side was strangely affected, the sense of cold appearing to lie internally upon the coating of the bones of the arm, thigh, and leg; and that, though the flesh externally was warm to the touch and generally in a state of perspiration, and though the skin appeared perfectly fresh and smooth, yet . . . the whole left side of my person was affected with a singular numbness to the touch."

Sir Philip was seen subsequently by Sir Astley Cooper, who diagnosed "an extravasation of blood upon the brain or its membranes." Further details are given in Guthrie's "Military Surgery."

"The concussion of the brain . . . . rendered the left half of his whole person incapable of resisting cold or of evolving heat. In a still atmosphere abroad, at 68° F., he said, 'the left side requires four coatings of stout flannel, which are augmented as the thermometer descends every two degrees and a half, to prevent a painful sense of cold, so that when it stands at freezing-point the quantity of clothing of the affected side becomes extremely burdensome.'"

Paucity of detail renders the century-old account less informative than is desirable; yet we may legitimately infer that the symptoms were attributable to a hæmorrhagic effusion, which is at least as likely to have been cortical or submeningeal as intracerebral; hence the case provides another example of thermal dysæsthesiæ of cerebral and possibly actually of cortical origin.

No case of *wetness* as a cortically arising dysæsthesia has as yet come under my notice, and I shall not now refer to those more elaborate forms of "subjective sensation," interesting though they are, constituted by hallucinations of the muscular sense—in which, for example, the Jacksonian sensory aura takes the form of a sensation of the arm moving or rising into the air, while in actual fact it does not thus move at all. More than one case of this rare kind I have had occasion to observe.

We have now concluded our sketch of the spontaneous or subjective sensations which make their appearance in association with organic disease at all physiological levels, from peripheral to cortical, and the

task that remains is to attempt a synthesis of their pathogeny and an investigation of their neural correlates, as far as may be practicable in the present state of knowledge.

(III) Pathogenesis.

Since the dysæsthesiæ with which we have been dealing are all conscious sensations, it follows without question in each and every instance that afferent paths from the site of the lesion to the "perceiving cortex" must be open, and that the latter itself, wherever perception originates therein, is in a state of integrity. If *cortical* disorder of function causes a dysæsthesia to arise in consciousness, the route from its particular site to the "perceiving cortex," and the latter, must be not disordered.

The pathogenic problem of irritation versus removal of inhibition or release of function seems unavoidably, perhaps, to arise at the outset—though whether these apparently opposite processes should be considered radically different is not at present altogether clear to me. It is incontrovertible that stimulation, excitation, or irritation can and does awaken dysæsthesiæ in consciousness. Direct stimulation of peripheral nerve-trunks (mechanical, chemical, electrical, etc.), causes pain, or, if weak, pain-like paræsthesiæ. Pressure, or a knock, on the ulnar nerve at the elbow invariably arouses painful tingling, and no other specific sensation. Noxæ of an organic (as opposed to inorganic) kind seem also to act definitely as irritants—witness the pains of any toxic or toxi-infective agent affecting peripheral nerves. At a higher level root pains must in many instances be of purely excitatory origin, if we believe at all that compression irritates. Local injections of strychnine into the dorsal horns of the cord give rise to severe pain in the corresponding segmental cutaneous zones (Dusser de Barenne) [21], while, according to Foerster, electrical stimulation of the antero-lateral funiculi results in pain, and of the columns of Goll in the cervical cord, in paræsthesiæ. Once more, direct excitation by electrical methods of the sensory cortex in conscious human subjects has often been shown to be accompanied by dysæsthesiæ, as already alluded to. Thus at all levels direct irritation of afferent systems must be allowed to be definitely algogenic or paræsthesigenic.

Again, the significance of the awakening or aggravation of dysæsthesiæ by extrinsic stimulation ought not to be underrated. Numerous instances of this have been met with by every clinician, and some have been narrated in the case-histories given above. If in a case of

causalgia momentarily latent the application of some dry or warm substance arouses agonizing pain, it can be solely by way of excitation, at least to all appearance.

On the other hand, the clinician tends to become dissatisfied, rightly or wrongly, with hypotheses which predicate the existence of persistent or permanent irritation, and, influenced by present-day neurophysiological conceptions, may seek rather to account for long-continued pains and dysæsthesiæ by some view explaining them as release-phenomena. To Sir Henry Head [22] we are indebted for an ingenious theory elucidating the central pains of certain thalamic lesions as release-phenomena rendered possible by removal of cortico-thalamic inhibition. We shall return to this matter shortly, but for the moment we must note the limitation of the conception to the pain-system and to thalamic cases. Whether it be not also of wider applicability is a point for discussion. Certainly I see no good reason why it, if accepted at all, should not also be utilized to account for persistent thermal and other dysæsthesiæ of central origin. That thalamic activity should be accompanied by consciousness for one variety of sensory experience, but not for others, is a difficulty for Head's theory not lightly got over, "essential organ of the thalamus" notwithstanding.

For the sake of clarity let us take a concrete instance of persistent thermal dysæsthesia. Only a short time since I saw once more the patient with syringobulbia (case reported by Wyllie) [10] referred to above, and ascertained that the dysæsthesia of icy coldness on the right side remains as before; it has now continued for at least six years. Of the existence of a left syringobulbic lesion involving, *inter alia*, the formatio reticularis of the left side of the medulla there can be no question. Does the dysæsthesia persist because the afferent fibres concerned with the conduction of the impulses underlying the sensation of cold (fibres anatomically interrupted by the lesion, since objective thermanæsthesia is present on the right side) are *in part* being "irritated" thereby, and the excitations interpreted in consciousness as a sensation of cold, with local signature? Or, alternatively, because a corticifugal inhibitory path, extending to the thalamus and beyond, is somehow impaired in function, allowing "hyperphysiological" afferents to pass to the thalamus and cortex? As for the latter conjecture, that of an efferent or corticifugal inhibitory system, it must extend lower than the thalamus if it is to be involved in the medullary lesion. What evidence is there of such descending inhibitory sensory systems, or what valid reason for the necessity or desirability

of such a hypothesis? "Irritation" of the afferent sensory system concerned by the existing structural bulbar lesion surely must appear an at least equally feasible explanation, if not much more so. However, the problem can be approached from a somewhat different viewpoint.

We owe to the profound researches of Head [22] the idea of a dual mechanism in the sensory system taken as a whole, and while his conclusions have not received general acceptance, it is curiously interesting that a number of recent workers seem to adopt some kind of dualism, though not in accord with the original subdivisions of the former, and with no unanimity among themselves. Thus Parsons [1], who (not entirely on the lines of Head) finds a fundamental contrast between what he calls "crude dyscritic sensibility" and "highly differentiated epicritic sensibility," declares that many facts "point to a dual mechanism at work in almost every domain of sensation, *with the exception of pain*" (italics mine), and is led to the conclusion that "Head's distinction of protopathic and epicritic systems is fundamentally correct in spite of grave difficulties and inconsistencies in detail." There is no trace here, however, or in Head's scheme, as far as I can find specifically, of any conception that in a Jacksonian sense the two form a pair of "corresponding opposites," and that one "antagonizes" the other—in other words, inhibits it. Foerster's latest contribution, however, to which I have several times already referred, embodies a theory of the following nature.

There is evidence, Foerster thinks, for the existence of two sensory systems: (1) *affective*, for the appreciation of pain and of pleasant and unpleasant qualities in sensation; (2) *perceptoric-epicritic*, for "pure sensation," viz., touch, pressure, warmth, cold, etc., unaccompanied by affective elements, and specially concerned with discrimination and spatial appreciation. Further, his speculation is to the effect that the former is normally regulated and inhibited by the latter; he concludes "dass normaliter das Schmerzsystem durch die gleichzeitige Erregung der Empfindungssysteme einer Regulation unterliegt, dass es einerseits eine Inhibition durch die Empfindungssysteme, andererseits eine Verfeinerung seiner Leistungen durch letztere erfährt." Consonant with this speculation, Foerster supposes one of the explanations of hyperpathia to reside in an overaction, a setting free, of the "pain-system," by impairment of the control normally exercised over it by the "sensation system." This is an ingenious hypothesis, though it obviously cannot cover all the clinical phenomena of hyperpathia, nor is it by any means universally applicable to the conditions we are considering, in

which, for example, one part or subdivision of Foerster's "sensation-system" itself is overfunctioning, or in which *both* systems are so in overaction (cf. the *burning* + the *pain* of causalgia).

But this is not his only idea of sensory inhibition. For spinal cases of "spontaneous" or central pains, he imagines that a corticifugal path extends right to the limiting layer in the lateral column, close to the dorsal horns, and that this path normally exercises an inhibiting effect on the pain-system cells of these horns. Similarly, he imagines the existence of a corticifugal inhibiting system extending to the brain-stem, which is out of action in cases of "central pain" at bulbo-pontine levels; finally he alludes to the Head and Holmes' view of a cortico-thalamic system of inhibition, accepting it as a possibility, but not declaring for it uniquely in explanation of thalamic pains. He considers, indeed, that thalamic activities are inhibited also from the corpus striatum.

Plausible as all this highly conjectural mechanism may possibly appear, after much consideration of the problems presented by the dysæsthesiæ I cannot see that it is either necessary or as explanatory as at first it may seem. I do not find it essential to posit an elaborate inhibitory system that passes out of action when painful or other varieties of dysæsthesia come into being. *Qua* pain, that of trigeminal neuralgia in no material way differs from central pain, and no one evidently is inclined to attribute it to removal by disease of an efferent pain-inhibiting system extending to the Gasserian ganglion; it can be explained more comfortably on the view that slow fibrous or other structural or toxi-infective changes in the ganglion irritate and excite the protoneurones. Where dysæsthesiæ are in evidence and objective sensory alterations cannot be detected, irritation of the sensory system and paths concerned seems to me quite feasible from the viewpoint of pathogenesis. If objective changes accompany the subjective phenomena, then the system involved is partly irritated and partly under destruction. If a form of anæsthesia dolorosa occurs (we might well use some similar expression for its analogues, such as subjective coldness with loss of appreciation of cold stimuli), we account for the latter by the block from the lesion, and for the former by "irritation," it may be, of fibres still capable of conducting excitations, which are misinterpreted by the cortex since they do not, as a fact, originate in cold applications. Obviously, at peripheral and at central levels, certain differences in the physiological process are to be expected.

The case is somewhat different, on the other hand, in respect of those examples (a few are given in this series) of subjective sensations of heat, or of cold, with objective loss of the *opposite* modality. Take concretely Case 7, in which subjective coldness was associated only with loss of heat appreciation. For cases of this category Hughlings Jackson [8] offered the following theory: "The superpositive element of the double symptomatology, the over-coldness, is not caused by any disease of the physical bases of the sensation cold; obviously it cannot be if the disease has produced, as we are supposing, a negative lesion. The continual over-coldness is consequent on removal of control, synonymously of inhibition, from the physical bases of the sensation cold, by destruction or by some negative lesion, of the physical bases of the sensation heat; there is a cessation of antagonism such that the nervous arrangements which are the physical bases of the sensation cold are 'let go,' and rise in activity . . . with an associated rise in the sensation cold, a continual over-coldness referred to the skin."

It should be remarked in this connection that Jackson's view is stated by him for cerebral cases only, and that he does not apply it specifically to cases with organic lesions at lower levels, though there appears to be no objection against its thus being applied. The hypothesis presupposes an innate or inherent antagonism or mutual inhibition, as between the two modes of sensation, hot and cold, being "corresponding opposites." As a part of a wider principle of physiological antagonism, the particular illustration given by Jackson bears closely on one aspect of the problems of dysæsthesia, yet its application must be allowed to be distinctly limited. As we have seen, clinical cases which do *not* substantiate it are no rarity. Again, the reader may recall that in one and the same case *both* correspondence *and* non-correspondence between dysæsthesia and loss of objective opposite can occur at the same time (cf. Case 12, and that of Gowler and Hope [11]). Once more, Jackson's hypothesis does not explain satisfactorily the objective loss of *both* modes of thermal sensibility in cutaneous areas where the patient has a subjective sensation of one only. Thus the patients in Case 9 and Case 13 (Marcet) felt neither the coldness of things cold nor the hotness of things hot over the region of the dysæsthesia of warmth or heat. While cold applications gave rise to a sensation of heat, hot applications felt neither hot (as they should have done accordingly to the theory) nor cold. I submit a possible explanation is that the existing subjective hot sensation in consciousness prevented the subject from appreciating additional hotness effected by

the application of hot substances to the skin areas concerned, on the one hand, while the loss of cold conductivity precluded the chance of their giving rise to a "false" sensation of cold on the other. We should also note the seeming failure of the hypothesis to explain the fact that, objectively, cold substances occasioned a sensation of warmth; that they did not result in a cold sensation follows from the destruction of the "physical bases" of that sensation, and one may presume their wrong appreciation is somehow connected with the existing subjective "warm" or "hot" dysæsthesia.

Thus so complex are the clinical possibilities that no unitary explanation covers all instances, apart from the consideration that physiological antagonisms in respect of other forms of sensory experience than the thermal do not suggest themselves with the same facility.

While, then, a pathogenesis by stimulation or excitation seems to present fewer difficulties and be less hypothetical than that depending on the existence of inhibitory systems, the possibility of the latter being a well-founded explanation for some of the phenomena is not to be lightly dismissed, and may yet find ampler evidential support than it would appear to have to-day. The theory according to which the spontaneous pains of the thalamic syndrome are caused by removal of inhibitory influence of cortex on thalamus is perhaps the least unattractive of the inhibition hypotheses; but I do not wish to leave this part of my subject without some allusion to an obstacle in the way of its acceptance. At the beginning I made the elementary remark that we can only know of our patients' dysæsthesiæ by their verbal description of them. This fact has been made use of by Graham Brown [23] in a criticism of the theory of cortico-thalamic sensory inhibition, and I cannot do better than quote his exposition. The theory implies that a psychical function (that of the appreciation of pain) is localized in a subcortical region, and that thalamic activity (at least under some conditions) is accompanied by consciousness thereof.

"We may leave aside the assumptions that the descending influence of the cortex upon the thalamus is one of depression, and of depression only, and that sensibility to pain is not affected by a lesion of the cortex, however large it be. There remains the fundamental obstacle that the patient in question was able to overact by *speech*. If the thalamus itself takes part in the mechanism of the overaction, *it must therefore still be in connection with the speech mechanism*. This fact forces us to one of

two conclusions. Either the motor speech mechanism lies in the thalamus, and the thalamus in that case itself 'said' that it overacted; or that mechanism lies in the cerebral cortex (or in some other region of the cerebrum than the thalamus), in which case the 'essential organ' of the thalamus turns out to be merely a portion of, or a relay station in, the path between receptor and motor speech mechanism. In this latter case the site of the overaction *may* be in the thalamus (if the lesion removes an inhibitory influence of cortex upon *thalamus*); or it *may* be in the cerebral cortex (if the inhibitory influence removed is one of thalamus upon *cortex*). . . . Even if we were able accurately to localize the site of the overaction, we should still be as far as ever from localization of the 'site of consciousness' for affective sensations. We may just as legitimately suppose it to be in the speech mechanism (or other motor mechanism) as in any preceding path of conduction" (italics in original).

We need not here enter on the question of "awareness" and degrees of consciousness, nor need we, at the same time, hesitate to entertain the possibility of psychical phenomena (of a graded kind) accompanying physiological activity at much lower levels than the cortex and in much simpler organisms than man, but as far as cutting off of thalamus from cortical control is concerned, it *is* connected with the cortex if the patient reacts by speech, and therefore *consciousness* of the sensations of pain *may* have another site than the thalamic "essential organ."

From various remarks already made apropos of a number of cases in this series, the reader will have gathered that another pathogenic factor than excitation or inhibition of neurones belonging to the nervous system proper may be responsible for some at least of the dysæsthesiæ. The association of one or other type with lesions (presumed or proved) either of the sympathetic nervous system or of the vascular system or both, is manifested in Cases 4, 5, 9, and 12, and may be justifiably surmised in others. I am myself convinced of the ætiological significance of the relationship, which is strengthened by knowledge of a number of other clinical illustrations (personal and communicated) which cannot here be reproduced in detail. By kind permission of Professor E. Archibald, of McGill University, Montreal, I am allowed to refer to an unpublished case of his, that of an elderly gentleman with persistent pain in the stump of an amputated thigh, for which all the usual medical and surgical procedures had proved unavailing until Professor Archibald performed a periarterial sympathectomy on the femoral artery in Scarpa's triangle, when the pain ceased and has never returned.

The lines of evidence may be marshalled somewhat as follows:—

(1) Blood-vessels normally are sensitive to pain. In Foerster's experience ligation of carotid, external iliac, vertebral, brachial and popliteal arteries is accompanied by pain. Fine neural networks have been demonstrated in the adventitia, and sensory end-plates on the external walls of arteries. The phenomena of migraine were shown many years ago by Lauder Brunton [24] to have a basis in angiospasm or vaso-constriction, while conversely migrainous pain ceases with the injection of angiodilators.

(2) Sensory nerves of vessels run in periarterial networks, passing therefrom at intervals to join main nerve-trunks (Kramer and Todd [25], Potts [26]). The possibility of a continuous side-path for vessel pain, constituted by afferent fibres which do not unite with nerve-trunks but pass directly to the sympathetic paravertebral chain, eventually to enter the neuraxis at higher levels, is denied by most but accepted by Foerster, who relies to some extent on the following experience of his own.

> The case was one of complete transverse lesion of the three lower roots of the brachial plexus (C7, C8, D1), with complete loss of all forms of cutaneous sensibility over the three ulnar fingers and the ulnar side of the hand. Deep pain, however, was preserved. Foerster exposed the nerv. digit. vol. proprius on one side of the little finger and stimulated it with a powerful faradic current, without the slightest consciousness of pain on the patient's part; but when he applied the electrodes to the corresponding digital artery the pain was intense.

It would appear, therefore, that three afferent pain paths may exist: (*a*) peripheral nerves, posterior spinal roots, cord; (*b*) vessel plexuses, peripheral nerves, spinal roots; (*c*) vessel plexuses, aorta, sympathetic paravertebral chain, white rami, posterior roots.

(3) The evidence furnished by cases of periarterial sympathectomy (Leriche [27], Müller [28], Platon [29], Quarry Wood [30], and many more) points undoubtedly to the modification of certain sensory disorders by operation on arterial plexuses, apparently by removal of angiospasm and development of relative hyperæmia. This clinical evidence must, in my opinion, be accepted, however obscure the exact mechanism of the production of the phenomena may still be. Indeed, an anatomist like Ranson [31] allows himself to say "it is impossible to explain the relief from pain which some patients experience after this operation" [periarterial sympathectomy]. In such instances, as in others, clinical research has preceded that of anatomy and physiology.

(4) In Case 12, as has been already narrated, pronounced dysæsthesiæ were present over a wide cutaneous region in which a concomitant angiospasm of central origin existed, so that pin-pricking did not result in bleeding. But with diminution in intensity of the "subjective sensations" return of bleeding on pin-prick took place. This association was much too definite to be merely coincidental, apart from the fact that it is borne out by cases of hysteria, as the following case, taken from a former article of mine [32], clearly proves.

The patient was a young woman, aged 22, with complete hysterical paraplegia, and with complete numbness of the legs corresponding. So absolute was the analgesia objectively that a needle was passed through the calf without its being perceived, and without causing any bleeding.

"After a strong application of the wire brush the analgesia entirely disappeared, and where a minute or two before she had felt nothing she now felt the needle instantaneously; and, in addition, *where formerly a vasomotor defect had prevented bleeding there was now bleeding whenever the skin was pricked.*"

These considerations, together with others which must be here omitted, do unquestionably point to the development of dysæsthesiæ (of some kinds) as a sequel to vascular disorder of sympathetic or of other origin. The clinician does not pay sufficient attention to the occurrence of venous neuralgia (cf. Edinger) [33], or of paræsthesiæ plausibly ascribable to changes in the vasa nervorum (cf. acroparæsthesia, *supra*). So far as precise knowledge takes us, on the other hand, it seems rather premature to assign the reception of pain *uniquely* to sympathetic nerve-endings in skin and muscle, as some are inclined to do. At the same time, we should not underrate the possible significance of the presence of unmyelinated nerve-fibrils as well as of myelinated fibres in most sensory end-organs (Agduhr and many others). Further, the histological researches of Boeke [34] and others appear to prove the existence of a sort of cell-syncytium in the end-organ, into which the periterminal network of fibrils passes by stages so gradual that it is sometimes difficult to say where fibril ends and cytoplasm begins. The possibility of sensory end-organs being influenced peripherally by local blood-states is, indeed, more feasible than a theory such as that of Trotter [35] would allow; according to the latter the nervous system is "insulated" from mesodermal (*inter alia*, vascular) tissues by various forms of laminated capsule (for the nerve-endings), and by perivascular sheaths (for the neuraxis). Histological discoveries rather militate against this view, as we have seen above at more than one stage in our discussion.

Summarizing, we may, I think, conclude that under certain circumstances a neural origin, under others a vascular or sympathico-vascular origin, underlies the manifestation in consciousness of tactile, painful, and thermal dysæsthesiæ.

The interpretation of dysæsthesiæ of a "mixed" type, such as that of "wetness," is more complex. Cases 2, 11, and 13 exemplify its genesis at peripheral and bulbar levels—so far its appearance at higher levels has not come under my notice. References to the phenomenon in the literature are peculiarly difficult to find. Parkes Weber [36] has recorded a case of splenomegalic polycythæmia in which the patient said that "whatever she touches with her hands (when her hands are cold, as they often are) feels wet to her." I have discovered a number of allusions to this "hygric illusion" or paræsthesia (sensation de mouillure) in older French and Italian literature (Ramadier [37], Mingazzini [38], Giannuli [39], Peli [40], Ravenna and Montagnini [41]). The majority of the reported cases concerned patients who were definitely alienated, and the phenomena were rather of the class of hallucination and presumably of psychogenic derivation. Attempts were made by more than one of these authors to "localize" the "hygric illusions" in the gyrus hippocampi, but the pathological evidence offered is unimpressive.

Introspectively, one may consider a hygric dysæsthesia compound of a tactile and a thermal element, to which an element as of "something moving" may perhaps be added. Immersing one's fore-arm in water one is conscious of: (1) a tactile "ring" at the level of its surface; (2) a sensation of warmth or of coolness; (3) a general sensation of touch-pressure over the whole cutaneous area immersed. When a patient describes the sensation as consisting also in a feeling of "something trickling" the element of "movement" certainly contributes to the whole complex. On the other hand, when (as in Cases 2 and 13) the complaint is of a feeling of wetness on the face I do not see that a thermal component is necessarily superadded, for objective perspiration can arouse this wet feeling, and in these circumstances it would seem that there must be patchy excitation of touch-spots over areas of measurable extent, and again, possibly, the above-mentioned feeling of "movement" on or over the skin. Relative juxtaposition at peripheral or bulbar levels of touch and thermæsthesia-conducting tracts may explain the origin of this complex dysæsthesia; at the level of the cortex their separation possibly prevents its occurrence as of "central origin"; and, theoretically at least, it should also on occasion be

thalamic, but I have found no reference to such, nor as yet encountered any such case personally.

As remarked at the outset, my purpose has been to deal mainly or solely with dysæsthesiæ in association with organic or structural conditions, and in consequence little has been said of the "neurasthenic" and "functional" varieties of "pressure," "crawling" (more generally, of formication), "drawing," "dragging," "tightness" ("as if in a vice"), etc., or of even more elaborate nature. Not that all or any of these are specifically "functional," for such is not the case, but one must set limits to the present discussion of a particularly wide-ranging and complicated topic. I have long been convinced of the desirability of observing and analysing the *apparently* spontaneous dysæsthesiæ described by what we call "neurotic" or "psychotic" subjects, and commend to the reader the philosophic interpretation of these undertaken a number of years ago by our present Hughlings Jackson lecturer, Dr. Charles L. Dana [42].

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DISCUSSION.

Dr. L. J. Pollock (Chicago) said he would attempt to deal from a clinical standpoint with part of Professor Stopford's contribution.

Some time after the severance of a peripheral nerve one could observe a recovery of the appreciation of pain in an area where there was no return of tactile sensibility. Some of this return of sensation to pain is certainly the result of overlap from adjacent nerves. This view is supported by the following observations:—

(1) The return of sensibility to pain prior to the recovery of sensibility to touch always occurs in certain areas peculiar to each individual nerve. In the case of the ulnar nerve sensibility to pain returns first in the proximity of the median area.

(2) When two adjacent nerves are injured simultaneously, sensation to pain never recovers before tactile sensation in those areas along their common border, where pain sensibility returns early when either nerve alone is injured. In combined palsies of the ulnar, median and radial nerves an early return of sensibility to pain is never observed in that part of the palm supplied by the ulnar or median nerve, and in combined ulnar and median lesions one never finds an early return of pain sensibility on the border between the anatomical distributions of these nerves. This law holds for all the peripheral nerves of the body.

(3) When an early recovery of sensibility to pain after section of a nerve, as the median, has occurred, and on exposure its ends are so widely separated that transplantation has to be performed and the radial nerve is used as a transplant, the area in which pain sensibility had returned becomes at once analgesic after severance of the radial.

(4) When sensibility to pain has returned within the sensory distribution of an injured nerve, resection and suture of this nerve produces no material difference in sensation in the area in which pain sensibility had recovered.

From these observations, which were made on over a thousand cases, it is obvious that the early return of sensibility to pain cannot be interpreted as a sign of regeneration of a nerve, but is due to the assumption of function by the overlapping of adjacent nerves which are not injured.

Dr. SCHWAB (St. Louis) said it was difficult to decide which points among the many that were brought up could be discussed with most profit, but he would select Dr. Kinnier Wilson's paper on paræsthesiæ, or so-called dysæsthesiæ. His remarks would be directed toward an attempt to widen the conception which these phenomena present.

In the many references this morning to the sensation of pain or discomfort the primary purpose of pain had not been touched upon—the physiological side of the matter seemed to have been totally neglected. Any logical attempt to study pain must always include the person who experiences it. There has been, in the speaker's opinion, too great a tendency to study pain and other related phenomena as if they were occurrences apart; the individual is left entirely out of the question. On the previous day problems of motion in experimental animals were largely considered; to-day, not the total human being, but a portion of

him has been dealt with. The problem of sensation must always be associated with that of awareness, and there is little possibility of experimenting upon an animal with the idea of studying this state. The interesting experimental work of Professor Sir Edward Sharpey Schafer, who made observations on himself as an experimental subject, is a striking exception to the usual method that has been presented during the last two days.

Dr. Wilson's paper is of striking interest, because he has not only brought out descriptively the phenomena of paræsthesiæ, but he has attempted, and in some instances succeeded, in correlating these sensations with certain definite regions of the nervous system. In other words, he has localized for clinical purposes the points of origin of these curious disturbing phenomena. Neurologists and others have to do largely in their practice with states of discomfort, often not typically painful sensations, which are described by the patient according to the powers of description which he happens to possess. It is consequently necessary to understand these symptoms as fully as possible, not merely from the standpoint of possible localization of lesions which are responsible for them, but for an understanding of what purpose they serve and why they exist. It is true that localization is often valuable, but less valuable than an appreciation of the purpose and object to the human body of sensations of discomfort.

It is a curious fact that at the beginning of an illness dysæsthesiæ have very often large or wide areas of distribution, and as the illness progresses there is a tendency for the area to become smaller and more localized and to become more sharply differentiated from the areas which can be regarded as normal. In some of these areas in which dysæsthetic sensations are felt, objective disturbances of sensation can be demonstrated, in others none whatever. This is a very important matter for observation. It is of the greatest importance to regard dysaesthesiæ as realities, just as objective disturbances of sensations are regarded as realities. Dysaesthesiæ are often the results of states of awareness of sensations arising out of crude sensations of internal organs, such as the intestines, bladder, lungs, &c., sensations which ordinarily do not reach the level of awareness or consciousnes. In states in which they are manifested as realities there is a lowering of the sensory level which permits the inrush of these sensations into the conscious levels of the patient. In this way they often form a valuable link in understanding the relationship which exists between them and somatic delusions. In a series of patients who presented somatic delusions it was found that in the early stages of their psychoses the state of awareness that has just been described was present, and that the crude sensations

which have been referred to passed over the lower levels of awareness and became subjective and real to the patient. It is often possible to create a sensation of dysæsthesia by simply directing the patient's attention to one particular organ or one particular segment of the body. By forcing a psychological concentration on a portion of the body which before had not been recognized in consciousness, that portion or that segment may be a fact recognized in consciousness as a definite area. The study of the phenomena of hypochondriasis affords support to this point of view, and an investigation of its mechanism shows that this disease is largely built up by sensations ordinarily below the level of awareness which suddenly or gradually become available stuff for consciousness to work upon. The spread of many of these curious sensations, involving further and further remote portions of the body, can be interpreted as a part of a system of defence reaction. Even when objective examination shows sensory changes beyond the anatomical limits of the parts involved, these can be often interpreted from the standpoint of the purpose underlying the presentation to the outside world of such sensations as those discussed by Dr. Wilson.

Dr. CASAMAJOR (New York) said that sensory disturbances have always remained less well understood than those of the motor systems, mainly because motor disturbances may be approached by purely objective methods of examination, while all sensory testing must be largely subjective, since the results must be interpreted from information which has sifted through the patient's consciousness, and they are hence liable to great inaccuracy. Therefore one is not surprised that sensation is less well understood than many other nervous functions.

Sensation arose as a neural function for the purpose of allowing the individual to be aware of the nature of his environment, and for this appreciation of environment to be efficient it must contain both qualitative and quantitative factors. The more of these factors present the more efficient is sensation. The simple contact sensations of lower forms was in higher organization supplemented by ability to receive and evaluate sensations from a distance by the development of distance receptors and the special senses.

Sensation and its disturbances may be considered on different, definite anatomical and physiological levels: (1) Reception—the level of the end organs; (2) conduction—the level of the peripheral nerves and cerebro-spinal pathways; (3) perception and reaction at the level of the cerebrum. Something of another level arrangement may be seen in the reactions to a painful stimulus. A painful stimulus applied to a part evokes first a withdrawal, a pure spinal response. This may occur

without perception of pain, as is seen in complete spinal cord lesions. Shortly following the withdrawal comes the thalamic response, the facial expression, the drawing in of the breath, and often sounds of an emotional nature. Still later, the cortical response—a description of the pain and how much it hurts.

It is interesting to speculate, as has been done so well this morning, on the levels at which differentiation between the various types of sensation takes place. It is known that different nerve-endings receive different modes of sensation. Professor Stopford has shown us that further differentiation may take place in the peripheral nerves; this is apparent in the different systems which recover at different times following nerve repair. He has shown that it is the more primative, protective forms of sensation—pain and temperature—that recover early. The discriminative forms return late, if at all.

Of course real anatomical differentiation occurs first in the spinal cord, where the fibres for the primitive affective sensations decussate early and pass up in the lateral columns, while those of discriminative, gnostic function pass directly to the posterior columns, not to decussate till they reach the bulb. Strong has pointed out that the first evidences of the anatomical patterning of sensation occur in the posterior columns of the spinal cord. The leg fibres are the most mesial and dorsal, the trunk fibres next and, still more lateral and ventral the arm fibres in the column of Burdach. When the face and head fibres appear, they lie ventral to those of the arm in spinal trigeminal root. This is the same dorso-ventral arrangement of localization that obtains in the cerebral cortex, and this resemblance is certainly not chance.

One feels that the function of neural relays in sensory pathways is in the interest of appreciation and understanding. Each relay probably raises sensation nearer to the level of perfection. After each relay the impulse is carried by a smaller number of fibres, probably by patterning combinations which reach their highest complexity in the cerebral cortex, there possibly forming the anatomical basis for consciousness.

To-day Dr. Kinnier Wilson has offered us another still more primitive type of sensory conduction along pathways in the sympathetic nervous system. For the comparative morphologist this should open up a wide field in the study of those most primative sensations which we have inherited from our earlier ancestors which possessed a ganglionic chain only.

Much of sensation remains to be elucidated, and we look forward to the solution of its problems in the hope and belief that the understanding of sensation will be a bridge to span the gap between neurology and psychology.

Dr. C. K. MILLS (Philadelphia) sent the following communication to the discussion :—

In 1888, I indicated my conviction that the sensory region not only was separate from the cerebral motor area, but was situated posteriorly to the Rolandic fissure [10]. Later, I began to speak of the sensory as encircling on all sides the motor region, and stated that each centre for movement had a topographically corresponding sensory centre [11].

Grünbaun and Sherrington, by their experiments on the anthropoids, clearly fixed the motor region as cephalad of the central or Rolandic fissure [3]. It must be remembered that the anterior slope of the central fissure is to be regarded as part of the motor area and the posterior slope of this fissure as belonging to the sensory area.

In a paper published in 1904 [12], I advocated the view that besides the major motor area in the precentral convolution, and cephalad of it, certain minor motor areas adjoined the regions for the senses of sight, hearing, equilibrium, smell and taste, as usually placed in diagrams of cerebral localization. In these minor motor areas movements immediately responsive to the sensory impression are presumably located. These minor areas are better developed in the anthropoids and perhaps in the young child, and are in time largely supplanted by the major or cutaneo-muscular area.

Ferrier [1], like myself, believed in separate sensory and motor localization. At first he placed sensory representation in the hippocampal convolution and the connected gyrus fornicatus or convolution of the callosum. Horsley and Schafer [7], as the result of their experiments on monkeys, also located sensory centres in the gyrus fornicatus. In his earliest published scheme, Ferrier indicated that the motor region was divided into practically two equal parts, one before and the other behind the central fissure. With others, however, he has come around to the view that the central fissure is largely the dividing line between motor and sensory cortical representation.

A knowledge of evolution is the key to a large part of our knowledge of natural phenomena, and nowhere is this more true than in the case of the human brain. The functions of the brain are the result of ages of development. It follows that to understand diseases of the brain its development must first be understood. More than this one should comprehend the views of Hughlings Jackson on dissolution [8].

Case after case of disease of the parietal lobe has been recorded by me—cases of tumour verified by operation or with necropsy, of hæmorrhage, softening, traumatism, abscess and arrest of development. These cases had as their main symptoms impairment or loss of cutaneous and muscular sensibility and astereognosis. I found that the muscular sense

was located more posteriorly than the centres for the different qualities of cutaneous sensibility, such as pain, touch and temperature and their derivatives. Starr and McCosh [19] early located the muscular sense in the superior parietal lobule.

I might say here a few words about the difference of opinions of capable observers on such symptoms as astereognosis. I placed the primary representation of stereognostic perception in the superior parietal convolution; others have put it in a more cephalic position, and some even in the precentral motor cortex. This difference of opinion is easily understood. In order that the form of an object may be easily recognized a comparison must be made mentally with previous tactuo-motor and visuo-motor perceptions. This is done through the employment of the associating tracts between the primary area of stereognosis and the motor cortex. If the motor cortex concerned with hand representation is destroyed or impaired, astereognosis therefore may result, but this does not mean that the stereognostic centre is located in the motor region.

I might here also say what I have stated in some of my contributions, that the division between the sensory and the motor cortex cannot be represented by a straight fence dividing two fields. The bottom of the Rolandic or central fissure is in large part the line of separation, but in the irregularities of evolution the line of demarcation may become jagged or irregular. At the lower extremity of the central fissure, in some cases at least, the sensory representation may extend forward into the precentral region. This is what might be expected when considering the process of surface evolution.

Foerster [2] has recently made a contribution to the question of cortical sensory localization as determined by him from observations on operation cases. His results seem to be entirely in accord with the views I have advanced in this paper, especially as regards the location in the post-central convolution of the representation of cutaneous sensibility.

In 1891, I reported a case of bilateral meningitis of the convexity with softening of both the cortex and subcortex of the parietal lobe of each side [13]. This case helped to demonstrate that common sensibility, including pain, touch, temperature, &c., is bilaterally represented. Reports of cases of this kind with necropsies are unusual. I believe with Head and Holmes [5] that the function of the sensory cortex is largely one of discrimination, but the sensory tests give varying results in different cases and at different times in the same case. In the case above mentioned of bilateral meningitis and softening, analgesia was complete and was variously distributed over both sides of the body. Unlike

what occurs in unilateral lesions, the analgesia was persistent and unchanging.

As early as 1889, in a paper on "Spinal Localization and its Practical Relations" [14], I called attention to the observations of Ross [16] on pre-axial and post-axial representation in the limbs. Reference was also made to the conclusions of Heringham [6]: "That of two spots on the skin, that which is nearest the pre-axial border tends to be supplied by the higher nerve, and of two spots in the pre-axial area the lower tends to be supplied by the lower nerve, and of two spots in the post-axial area the lower tends to be supplied by the higher nerve." Dr. Weisenburg and the writer examined the hand in several cases and found in some of these marked differences between the radial or pre-axial, and the ulnar or post-axial, portions [15]. Objects could be recognized promptly by the finger and thumb which were not appreciated, or only very imperfectly, by the little and the ring finger or the middle finger.

Russel and Horsley [18] made an important contribution on the apparent representation in the cerebral cortex of the type of sensory representation as it exists in the spinal cord. Their observations were of unusual interest on topognosis, or topographical representation. They discussed the subjects of post-axial, pre-axial and mid-axial representation in the limbs.

Head [4] makes, however, the strong point that such terms as pre-axial, post-axial and mid-axial must be accepted with reservation when applied to the study of the functions of certain restricted portions of the sensory cortex.

Applying his ideas to the fingers and hand, Head argues that the thumb and each of the fingers is represented separately in the cortex, and this representation can be demonstrated in special cases. Of course, it may happen that in the sensory cortex a lesion may be somewhat diffuse, in which case the effect on the periphery might be either pre-axial or post-axial. On the palm of the hand the parts affected would correspond to the thumb and each of the digits, according to the cortical lesion. Of course, when the lesion is a large one in the arm area all parts may be affected.

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Dr. WEISENBURG (Philadelphia) pleaded for the adoption of an uniform method of examining and recording sensation and its disorders. One of the most important contributions made by Head and Holmes was their methods of examination. In evaluating the results arrived at by different observers, the methods employed must always be taken into account. More work ought to be done on the sensibility of normal persons as there was too great a proneness to draw conclusions from pathological material, in the absence of a consideration of the behaviour under similar circumstances of a normal individual.

For instance, one of his students, G. Pearson, made a study of vibratory sensation, and found that in normal persons who had reached or passed their 50th year, sensibility to vibration diminished, so that after that age absence of the ordinary response could not be regarded

as pathological. This may conceivably be true of other forms of sensation too. It was his intention to devote considerable attention to the examination of sensibility in normal persons.

The importance of first trying tests on normals was shown by Alpers and Pearson, two of his students, who repeated Head's aphasia tests. The subjects selected were ten students of neurology who were of superior intelligence, and fairly good neurologists. On repeating these tests on these ten students it was found that some of the responses were similar to those which Head got in his pathological subjects.

It has been repeatedly stated that in patients with certain motor diseases there may be no disturbance of sensation; but he had seen patients with progressive spinal muscular atrophy and poliomyelitis who, though there was no disturbance of subjective or objective sensibility, nevertheless complained if an object struck their involved parts of a great amount of resultant pain, as if the threshold of sensibility had been lowered. Loss of vasomotor tone may be responsible for this.

He was particularly interested in cortical sensation, and was in general agreement with the work of Head and Holmes. He believed, however, that primary sensation was chiefly localized in the post-central convolution and muscle sensibility in the parietal lobe. And he agreed with Holmes that hysterical manifestations were common in organic lesions, a point not sufficiently emphasized.

Dr. Schwab struck a sympathetic note when he said one must consider the reaction of the person at the time of the examination; patients are human beings, not objects in which the psyche need not be considered.

With regard to peri-arterial sympathectomy, there had been many instances of atypical facial pains for which various explanations had been offered, including Sluder's. There had now been advanced another explanation for these so-called atypical pains, i.e., sympathetic involvement. In Philadelphia Frazier, within a few months, reported twelve cases of this sort in which he stripped the carotid of its sympathetic fibres without relief of the pain.

Professor PETRÉN (Lund) said it gave him the greatest satisfaction to hear Professor Stopford and Dr. Gordon Holmes, who, starting from different points of view, had arrived at the same conclusions. It must be recognized that the ideas they had advanced were especially due to the initiative of Sir Henry Head, and it was a pleasure to find that his investigations had been so widely accepted.

Dr. Wilfrid Harris spoke of sensory conduction in the spinal cord, and gave a general review of many interesting personal observations,

but he had some difficulty in following his views on sensory conduction. He understood him to say that tactile impulses decussated slowly in the cord. He could not entirely agree with this. His own investigations, which were published twenty-five years ago, consisted in a clinical analysis of all the published cases of stab wounds of the spinal cord, in which it is true the exact site of the anatomical lesions could not be always determined. From these investigations he concluded that tactile sensibility uses two paths in the cord, one in the neighbourhood of the paths for pain and temperature conduction in the opposite lateral column, and another in the posterior column of the same side. Dr. Harris has not adduced any arguments against these conclusions, which are now largely accepted.

If tactile sensibility has two different paths in the spinal cord, it is natural to inquire if these paths are not concerned in the conduction of different kinds of sensibility. Fabritius has attempted to find evidence of such a differentiation of tactile sensibility in the cord.

According to the phylogenetic investigations of Brouwer the posterior columns are a much younger part of the spinal cord than the antero-lateral columns. This suggests that the posterior columns conduct discriminative elements of sensibility.

Professor BROUWER (Amsterdam) pointed out that much had been done from the comparative anatomical point of view in regard to function and sensation. In Holland they constantly employed the methods of Head and Holmes when examining cases of brain disease, and the work of Petrén when studying lesions of the spinal cord.

The posterior columns convey sensation of touch and of deep pressure; the lateral columns, pain and thermal sensations and tactile impulses, too. In descending the animal scale the posterior columns become smaller and smaller. In the bird they are very small, and the lateral columns much larger, while in fishes the posterior horns lie so close together that almost no posterior column fibres exist, and there are no nuclei of Goll and Burdach. Therefore he had arrived at the idea that the first pathway for sensory stimuli was that in the lateral columns, the spino-thalamic tract of Edinger, which already exists in fishes. Later a new pathway developed in the posterior columns. These facts point to there being two groups of sensibility, an older form conveyed through the antero-lateral path, and a newer form in the posterior columns.

Higher in the animal scale the posterior horns are not always identical in structure; they are very simple in lower animals, but more complex in mammals, and particularly in man. The older form of

sensation was always combined with movements of organs innervated by the sympathetic system, and all the stimuli entering the posterior horn were connected with the sympathetic centres. The same relationships could be found in the brain-stem of many animals he had studied. In fishes there was only a spinal trigeminal root; therefore all the sensory stimuli were conducted through it. The frontal trigeminal nucleus, which develops later, is a homologue of the nucleus of Burdach.

He has endeavoured to give a biological conception of the organization of sensation. In addition to a more primitive lateral column system there is a newer form of sensibility, conducted in the posterior columns, which is not associated with sympathetic activity. Dr. Kinnier Wilson's studies had subdivided the motor apparatus into palæo-motor and neo-motor systems, and it seemed that a study of sensation on anatomical lines would achieve the same result for the sensory system. These studies in comparative anatomy helped in the elucidation of the sensory problems encountered in clinical work.

SHORT PAPERS.

SYMPTOMATOLOGY OF A GROUP OF FRONTAL LOBE LESIONS.

BY ERNEST SACHS, M.D.
(*St. Louis, Mo.*)

THE recognition of frontal lobe lesions, particularly of the right frontal lobe, offers unusual difficulties. This has been due, of course, in part to the fact that the frontal lobes give rise to such slight symptoms, and also, to a very great extent, to the fact that the classical symptoms, at least in our experience, are not observed as frequently as the literature would lead one to believe. As I have followed my frontal lobe cases there are two symptoms that have stood out more prominently than any others, and I have come to depend on them more than upon any of the classical symptoms.

The present communication is based on a series of twenty-five frontal lobe lesions which have all been verified by operation or autopsy. Fifteen of these were on the left side and ten on the right side. The symptoms that have been emphasized by other observers as of particular diagnostic value are the emotional changes, eye-ground changes, particularly primary optic atrophy on the side of the lesion with choked disc on the side opposite, unilateral tremor of the hand and arm on the side of the lesion, loss of the abdominal reflex on the side opposite the lesion, anosmia on one or both sides, and speech disturbances. Where the lesions are large enough to involve or press upon the pyramidal tract, symptoms from that source may be expected.

This group of twenty-five cases has been analysed with the idea of determining which symptoms are most valuable for purposes of localization. Of the general symptoms of headache and vomiting and occasional symptoms, as adiadochokinesis, I shall say nothing since they have no localizing value ; their occurrence has been recorded in the table that is appended.

In the twenty-five cases there were ten gliomata, seven endotheliomas, two gummas, two abscesses, one arachnoidal cyst, one chronic inflammatory mass around a foreign body, one basal cell carcinoma, and one degeneration of the frontal lobe. Two of the patients with endotheliomas died, and four with gliomata. One of these was not operated

and died of pneumonia shortly after coming into the hospital. I shall first consider what I have called the classical symptoms.

Emotional changes were noted in but seven cases, and impulsive laughter or crying which, from the literature, one is led to believe is such a common occurrence, was only noted in five cases. In fact, this symptom was so rarely encountered that it could not be depended upon. When present, however, it is of great value since it is so characteristic.

The eye-grounds showed no changes that can be considered of localizing value. Eleven of our cases had double choked disc, while six had normal eye-grounds, and three blurring of the disc margins only. In not a single instance, however, did we note primary optic atrophy on the side of the tumour with choked disc on the opposite side, as described by Foster Kennedy, and we had but a single instance of a central scotoma which others have observed frequently. I am somewhat at a loss to account for this difference in eye findings. Twenty-five cases are a small number to generalize from, yet a symptom that is noted in but a single instance must be of doubtful value. In only five of the twenty-five cases did the visual fields show any abnormality; in each of these there was a partial homonymous hemianopsia due to the encroachment of the lesion on the temporal lobe. These homonymous defects, often very small in size, were of the kind that Cushing first drew attention to. These only can be discovered when very careful perimetric studies are made. The defects sometimes only cover an area of 15° and consequently the field must be taken every 15°.

Unilateral tremor was noted but five times, twice on the side of the lesion and three times on the opposite side. When it was observed, it resembled the type of tremor described by Stewart.

A difference in the *abdominal reflexes* was also found in a very small number of cases, seven times; six times on the side opposite the lesion and once on the side of the lesion. In six cases the patients were so stout that no abdominal reflexes could be elicited.

The *deep reflexes* were normal in eleven of the cases, and in nine the only pathological reflexes were an Oppenheim and Babinski, while five cases showed more marked pyramidal tract involvement.

That so many cases had normal reflexes was due to our seeing the cases at a time when not enough intracranial pressure had developed to involve the pyramidal tract. The fact that the abdominal reflexes were so rarely disturbed may be explained by the fact that a number of the lesions were at or near the under surface of the frontal lobe. However, the abdominal reflexes were not involved in several cases where the lesion was in the frontal lobe near the longitudinal sinus, where one would expect to have disturbance of the abdominal reflexes.

Smell was normal in nineteen cases and lost but twice. In three

other cases there were subjective smell disturbances, and in at least one of these there was a definite involvement of the temporal lobe which doubtless accounted for this disturbance.

Speech disturbances were present in thirteen of these twenty-five patients. Of the fifteen patients who had left-sided lesions, ten showed a speech disturbance, while the other three instances occurred in patients with right-sided lesions. These speech disturbances varied to such an extent that classifying them has been almost impossible. However, aphasia was always of the verbal type. In a few cases there seemed to be purely nominal aphasia. In a few cases the only disturbance was a hesitancy and slowness of speech, but the most careful study revealed no other affection. It may be open to question whether we are justified in calling a mere hesitancy and slowness of speech a form of aphasia. In these patients it was impossible to detect any verbal or sensory speech defect. The reason for this slowing could not be determined, as most of the patients could not explain why they had become more deliberate in their speech. One very intelligent woman volunteered the information that she had trained herself to speak slowly, as she had noticed that she occasionally confused syllables or started to use the wrong word, and found that by speaking slowly this did not happen. It is not unlikely that this hesitancy in speech may be the precursor of an aphasia.

X-ray findings were of value in only ten of these twenty-five cases. Ventriculography was only attempted in six cases, and in none of these did it show definitely where the tumour was located, though in all six the ventricles were collapsed, which, of course, is to be expected in frontal lobe lesions. This collapse of the ventricles, however, did definitely help in one case that had been diagnosed first as a cerebellar tumour and who had had two posterior fossa explorations. Even in this case, however, the air injection did not indicate the side of the lesion; this was determined by the neurological symptoms and physical signs.

From this brief summary it is quite evident that the classical symptoms ascribed to frontal lobe lesions were only noted in about half the cases. Realizing this great deficiency, we searched for other evidence and find that we have been basing our diagnosis of a frontal lobe lesion on two other symptoms which we have found are much more frequently present. The first of these is a slight *weakness of the lower portion of the face*, that innervated by the two lower branches of the facial nerve on the side opposite the lesion. This was noted in twenty of the twenty-five cases. This is not an emotional facial disturbance, nor could it always be demonstrated on voluntary movement; it was usually most obvious during conversation with the patient, and was in the nature of a drooping or lagging of that portion of the face. In a

number of instances we were told the patient had always had this lagging of the face, yet after the tumour had been removed it disappeared. We have come to attach considerable importance to this slight paresis of the face. No doubt it is a pressure phenomenon and is due to involvement of the face centre. The reason, I presume, that this paresis occurs more frequently than a difference in the abdominal reflexes is because the face centre is more highly specialized and therefore more sensitive.

But the leading symptom that these cases showed which far outweighs all others is the *mental change*. In twenty-one of our twenty-five patients this was observed. This mental disturbance, we believe, is so characteristic that it is possible to distinguish it from the mental change that occurs in any other type of nervous disorder. As I have watched these patients, the changes that have seemed to me particularly characteristic are the following:—

Patients are peculiarly indifferent, they seem to have no realization of the seriousness of their condition, and if told they require an operative procedure do not worry about this at all. When asked why they do not worry, they not infrequently shrug their shoulders. At the same time they are not euphoric; there was only one patient in our whole series who showed any tendency to be so. Their loss of memory pertains particularly to recent events, while their memory of past events may be quite good; for example, an individual was brought to St. Louis from Texas, which is about a twenty-four hour journey, and the morning of his arrival he stated that he had been in St. Louis for four weeks but did not know the name of the city. He, however, remembered perfectly distinctly the number and name of the street where he had lived several years ago in the city in Texas from which he had come, but did not remember his present address in that city. A loss of memory for recent events was noted repeatedly while memories of occurrences several years before were quite vivid in such a patient's mind. Occasionally patients recall after operation the disturbance in memory that they had had. For example, one such patient stated that his memory had been hazy and that he felt as if he had been living in a fog which now had cleared up. Two other individuals, one a druggist and one a farmer, had lost all interest or enthusiasm in their work. The farmer had neglected his cattle and his farm implements, and following removal of the tumour both he and his wife noted that his former interest had returned. In the same way, the druggist had become indifferent, had not kept up his stock of drugs, had allowed his place of business to run down, and had not been concerned whether his business was paying or not. After operation this indifference disappeared and he displayed the same interest that he had before he was taken ill.

This mental disturbance, when present and unchanged for some time, and associated with some facial weakness and headache, in the absence of a positive Wassermann, indicates a frontal lobe lesion and entitles the patient to an exploration. Operation has repeatedly revealed a focal lesion, usually a tumour, in the frontal lobe.

SUMMARY OF CASES AND SYMPTOMS.

Number of cases of frontal lobe lesions		25
Number of cases operated	24	
Number of deaths (one of these not operated)	6	

Type of lesion.

Glioma	10
Endothelioma	7
Gumma	2
Abscess	2
Arachnoidal cyst in region of Sylvian fissure	1
Chronic inflammation and foreign body	1
Basal carcinoma	1
Degeneration of frontal lobe	1

Side of lesion.		*Headache and vomiting.*		*Right or left handed.*	
Left side	15	Headache	19	Right-handed patients	24
Right side	10	Vomiting	12	Left-handed patients	1

Ophthalmoscopic findings.

Normal eye grounds	6
Slight blurring	3
Distinct difference between two sides	4
(On side of lesion 2)	
(On side opposite lesion 2)	
Choked disc, bilateral	11
Unilateral atrophy	0

Visual fields.

Normal fields	6
Partial homonymous hemianopsia due to encroachment of tumour on temporal lobe	5
General contraction due to high grade of choking	4
Central scotoma	1
Could not be taken because of lack of co-operation of patient	10

Convulsive movements.

Focal convulsions	6
General convulsions	6

Nystagmus.

Nystagmus, lateral	3

Motor changes.

Hemiparesis, varying from slight involvement to almost complete hemiplegia	11
Facial weakness on side opposite lesion	20
Facial weakness only, with no other motor paresis	12
Weakness of arm or leg without facial involvement	3

Reflexes, upper and lower extremities.

Normal reflexes	11
Pathological reflexes :—	
Oppenheim and Babinski, but no other pathological reflexes	9
Ankle or patellar clonus in addition to Oppenheim and Babinski	5

Reflexes, abdominal.

Normal reflexes	11
Not obtained on either side due to fat abdomen	6
Diminished on side opposite lesion	6
Diminished on side of lesion	1

Sense of smell.

Subjective disturbance of smell	3
Loss of smell, both sides	2
Loss of smell on side of lesion	3
Sense of smell normal	19
Could not be tested	1

Unilateral tremor.

On side opposite lesion	3
On side of lesion	2

Adiadochokinesis.

Adiadokokinesis on side opposite lesion	1

Speech disturbances.

No speech disturbances		12
Speech disturbances		13
(Verbal aphasia, marked	5)	
(Verbal aphasia, slight	2)	
(Nominal aphasia	2)	
(Nominal aphasia, with slurring and clumsiness in word expression	1)	
(Hesitancy and slowness in speech	3)	

Mental changes (including emotional changes).

No mental changes			3
(Gumma	1)		
(Abscess in a child	1)		
(Endothelioma	1)		
Mental changes			21
(Emotional changes	7)		
(Impulsive laughter or crying	5)		
(Very morose	1)		
(Indifferent	1)		
(Mental changes other than emotional	14)		

X-ray findings.

Plates showed shadows interpreted as tumour shadows	7
Plates showed pressure skull	3
Plates showed foreign body	1
Plates showed no X-ray changes	14

Air injection.

Air injection was undertaken in 6 cases, but in only 3 was air put in; none of these gave definite confirmation of diagnosis; all 6 showed collapsed ventricles.

One case was first diagnosed as cerebellar tumour; this patient would have been spared the cerebellar operations had the air injection been done first.

CHANGES IN PERSONALITY IN TUMOURS OF THE FRONTAL LOBE.

BY SIDNEY I. SCHWAB.

(*St. Louis, Mo.*)

THAT the frontal lobes have a great deal to do with psychical functions is almost a neurological tradition. Evidence in favour of it has been accumulating for a long period of time and is based mainly upon numerous cases in which various lesions of the frontal lobes have been accompanied by striking alterations in the psychical characteristics of the individual. It is no longer believed, however, that the frontal lobes are the only or perhaps the main sources of activities of this nature. The observation that among the symptoms produced by lesions in this region of the brain is a change in the personality and an alteration in the social function of personality, that is behaviour, has been supported by a mass of clinical observation that seems conclusive.

It is not necessary in this brief communication to furnish citations from the literature. Two observations supported by general experience will be sufficient to emphasize the facts stated. The first is that dementia paralytica, which is perhaps the best understood of all psychiatric conditions in so far as the underlying anatomical changes are concerned, and in which diagnosis is more certain than any other mental disease, shows predominant changes in the frontal regions, often almost to the exclusion of marked alterations elsewhere. In this disease changes in personality may be among the first manifestations. The second is that injuries to the brain in which the frontal lobes are mainly involved develop the most profound psychical changes, and the most definite alterations of personality.

The fact that one of the most important functions of the mechanism of speech has its anatomical basis in the left frontal lobe brings that faculty into intimate relation with the development of psychical levels of a high order. Defects in the emissive element of speech, which may be regarded as its most specialized social function, must inevitably produce psychical alterations of a profound kind. Speech may be regarded as a typical function of the frontal lobe, and it represents the most important single element in the upbuilding of psychical structure.

Embryological evidence, anatomical study and clinical observation

all suggest that the frontal lobes are concerned, primarily or not, with the development and the impetus towards psychical functioning. Whatever notion of cerebral localization is accepted, the participation of the frontal lobes in activities that are commonly spoken of as psychical must be admitted. The frontal lobes are in no sense to be considered the sole regions where such functions have their origins. They may be regarded as concentration points where, for reasons of anatomical and physiological efficiency, specialization has come about. The presence of a motor mechanism easily adapted to the emissive factor of speech makes of this region a locality where development can most favourably proceed. There is no need, therefore, to assume any narrow theory of cerebral localization; nothing in the nature of an anatomically limited or restricted centre should be seriously considered. It is only necessary to assume that on the whole the frontal lobes are immediately concerned in the origin, development and maintenance of such functions of the brain as are predominantly psychical as contrasted to the responses that are physical. That these two are intimately correlated, and that no separation or delimitation can be made out in many instances, is freely admitted.

The special task of this paper is the consideration of one of the most important, perhaps the most notable, of the functions of the mind, that is personality. In regarding personality as a product of psychical activity there is no desire to define it as a manifestation of this alone; the implication is rather that the synthesis of personality is largely a product of psychical formulation. All mechanisms of the body are involved in it, but it is the psychical activities that make of personality something that can be tangibly observed and that can be brought into the region of careful study. I propose, therefore, to attempt to define the term personality, to analyse its important elements, and to try to use it for the purpose of diagnosis and localization. The material that Dr. Sachs has just presented, part of which I have been permitted to study, and cases in which operation has not been feasible or in which the diagnosis of tumour has not been made, or instances in which at post-mortem examination lesions of the frontal lobes of inflammatory, vascular or infectious nature were found, form the basis for the statement that frontal lesions cause psychical alterations, and that one of the outstanding features of this alteration have been changes in personality. Often, indeed, this symptom has been the most striking evidence of the changes going on in the brain, and has so dominated the picture that for a time at least it was mainly responsible for calling the attention of the patient and of those about him to the fact that an illness was present.

In order to make use of a system of this kind it is necessary to formulate some notion of what it is. What is meant by personality, how is it made up and how can it be used in diagnosis in such cases as those upon which this communication is based? These are some of the questions that must be answered. To define personality satisfactorily is a task beyond the scope of this paper and beyond the ability of its author. To give a definition that may be of clinical use is however possible, and if it meets the test of clinical application the definition, though limited, may be seriously considered.

In the first place personality suggests differentiation; it deals with this rather than similarities. Personality immediately suggests the analogous term individuality, but this has more to do with purely physical differences, and the sum of those differential features that delimits one person from another, and one type of physical conformation from another. Personality is akin to this, but its implication is not only deeper but broader. There is a distinct social implication in personality that individuality lacks. Personality not only suggests the quality of difference, but the intangible shadings of these differences. There is something that is associated with the highest functions of the nervous system, something that becomes manifest only to a mutually sensitive perceptive organization. Personality then is the product of the play of psychical functions in and about the physical traits of differences. These functions arise out of and are stimulated into activity by consciousness. Personality then might be defined as the projection into the external world of the inherent or acquired elements which make up the physical conformation of the individual, organized into a composite picture through the synthetic action of consciousness. It is the replica of the totality of the organized traits, qualities, activities and other functional responses built about the physical conformation that produce as a final result identity. It is a development of individuality in which there is a dominance of psychical qualities. These various aspects of personality are necessary in order to create a conception that will embrace as many of its variables as possible and give to its clinical aspect as many points for study as can be conveniently made use of. On the basis of these conceptions it is possible to separate out many of the factors concerned, both for the purpose of identifying and of making use of them in a clinical study of patients in whom lesions in the frontal lobes cause changes or alterations in personality.

Personality is made up of physical and psychical elements and combinations of them. Some of these elements can be analysed, studied and recorded descriptively in the clinical history of a case, much in the same fashion as any other series of observations. Such a study may con-

veniently be divided into four main heads: (1) Purely physical traits; (2) physiological traits; (3) psychical traits; and (4) a group for which it is difficult to find an adequate term, but which can be understood if the word "flavour" is used. It is the last group that presents the chief difficulty in tabulation. The object in attempting to construct a personality under these four headings is to find a standard of comparison either for the period before the change in personality had been noted, or in successive stages during the progress of the disease. Only a mere sketch of the possible observable data will be mentioned, but enough to indicate the lines along which inquiry should be made.

Under the heading of physical elements would be included such facts as skeletal type, largeness, smallness, proportionate development or the lack of it, regularity of features or the reverse, variations in colour, growth of hair and its distribution, prominences, hollows and other surface characteristics, and many of the features that distinguish one individual from another as far as physical traits are concerned. Racial physical patterns as well as attitudes, postures and the type of gait, which depend purely upon anatomical observations, should also be included. The purpose of this part of the study is to suggest the physical pattern upon which personality is built; it is the groundwork that presents the physical differentiated type. Changes in this aspect of personality due to lesions of the frontal lobes may produce a difference in external appearance that may have an important bearing upon the final personality picture.

Under the physiological elements all those qualities which are predominantly active, as opposed to the static group just noted, must be included. The physiological characteristics of personality have to do with the mechanism in action, and include speed, promptness, accuracy and grace of movement; the strength and time relations of responses, as well as suppleness, clumsiness and direction in simple or complex motor acts. The characters of response and of movement depend on both the static pattern and the pattern of action. Either of these, that is the anatomical or the physiological, or both, furnish the basis for individual differences which, as far as outward traits are concerned, distinguish one person from another. The anatomical and the physiological aspects of a human being give the observer a set of impressions that cannot fail to be coloured with some sort of a feeling tone. These emotional reactions, slight though they may be in some instances and pronounced in others, are the beginnings of a higher order of response between individuals, and thus are the initial stages of synthesis of personality without the sacrifice of identity. Changes in this picture due to disease, especially of that nature which alters the well known patterns

of function associated with a certain individual and with him alone, are often striking enough to attract attention. Lesions in the frontal lobes cause, or may cause, through direct or indirect influence on motor control, such a change in the type, character and quality of movement that the previously sharp outline of a known figure may become shadowy and vague. He is said to have altered, his personality is said to have changed, he is like another person. All this may depend upon nothing more than a physiological alteration, or what may be more clearly described as change in the pattern of function.

The third of the catagories includes the characteristics that make up the mental activities of an individual; it is his psychical expression. It includes all the factors capable of description out of which his conduct grows and from which his social responses are made up. All that is here possible is an outline or sketch of another person's mind in order to determine for comparison with a previous outline his mental characteristics. In the study of personality such data are of great importance, and by this means the progress of a lesion can best be measured, and the rapidity of its growth and the extent of its involvement can be indicated more rapidly than in any other way.

There is no need to discuss the various faculties that are said to make up the mind. A much more practical approach is through the observations of certain functions of intelligence as speech, memory, understanding, imagination, judgment, appreciation, and the capacity to arrive at conclusions and deductions from a set of observations. The study of speech is especially important; its richness in vocabulary, poverty of expression, quality of vocalization, slowness of utterance, choice of words, sentence formation, narrative sequence and other varying qualities should be daily noted. After a few carefully planned conversations observations of value may be secured. Points of view, ethical considerations, artistic appreciations, &c., may be obtained which indicate the predominant qualities of a mind as it presents itself under the limitations of hospital or medical scrutiny. It is always important to realize the obvious and necessary limits of such a mental survey, the aims of which are merely to obtain a comparative estimate of the intellectual resources, as a contrast to the picture that may be furnished by some one whose knowledge extends far enough back in the life of the individual. Complicated analyses such as are in vogue at present, and aim at the discovery of complexes buried deeply in the lower levels of consciousness, are not necessary. A composite picture of the outlines of personality as an intellectual phenomona is all that is needed. Such items are commonly gathered together in a typical social survey of an individual.

The last category includes the general impression that the personality makes, as pleasing, disagreeable, revolting, suspicious, charming, &c. These are often, it is true, the mutual reactions that take place between two individuals, but though impressions differ a good deal and may seem unreliable, those qualities that are attractive and displeasing, even if they are intangible, will be found to be surprisingly uniform in their effects. In a series of observations it is striking how frequently the personality registers similar effects upon different observers.

From observations collected under these four categories it is not a difficult task to sketch briefly the personality of a patient who is suspected to be a victim of a lesion in the frontal lobes. A sketch thus made can be presented to those who have known the patient previous to his illness, and if a change has taken place it is an easy task to determine in what category it falls. If a progressive lesion, as a tumour, is present, the change in personality can be observed from time to time, and an indication obtained of the rapidity of its growth. In tumours of the right frontal lobe in right-handed individuals, the value of the personality alteration is often very great, as in the absence of speech involvement the diagnosis, or even the side of the lesion, is often uncertain.

It is unnecessary to emphasize the fact that alteration in personality is only one of the symptoms of lesions of the frontal lobes. The aim of this contribution is to reduce a clinical expression that is used vaguely to something more concrete and more tangible. Change in personality are in this way easy to demonstrate, simple to record, and capable of identification, and when recorded can be scrutinized and studied critically as other more objectively obtained data.

DISCUSSION.

Dr. GORDON HOLMES said he had been very interested in the presentation of these valuable contributions on the difficult subject of the diagnosis and localization of lesions of the frontal lobe. He had had an exceptional opportunity of seeing a large number of such lesions, as hundreds of men who sustained gunshot wounds of the frontal lobe during the war came under his observation. There was no doubt that the conclusions these two authors had come to were justified. The mental symptoms were, in certain cases, very prominent, though in some cases they were absent. But that held for all the signs one could speak of as belonging to the frontal lobe, as it was not a single mechanism, but consisted of different parts, probably with different functions. To complete this study it would be necessary to outline the definite changes found, either in mind or in body, in relation to the position of the tumour in the frontal lobe. For instance, optic atrophy or disturbances of the sense of smell can be expected only with basal lesions which involve directly or by pressure either the olfactory bulb or tract, or the optic nerve. It was in

that type of case that Gowers, and later Foster Kennedy, described the combination of optic atrophy on one side and papillœdema on the other.

The speaker had no doubt of the value of the two symptoms brought out in Dr. Sachs's paper, and especially of the slight asymmetry of the face, the slight tendency to drooping or lagging in early movement of the side opposite the lesion. Still, he was surprised to hear that it was practically constant in the twenty five cases.

He would point to one other symptom that is occasionally present, but it must be remembered that no symptom can be constantly associated with lesions of such a large area of the brain. It is known from physiological experiments that there is, chiefly in the second frontal convolution, a large area of the cortex concerned in the movements of the eyes. It is true that in lesions of the frontal lobe one can never, to ordinary testing, determine a definite ocular palsy, or even paresis on deviation of the eyes in one direction. Patients can follow an object or look fully to either side, but if the examiner stands in front of the patient and gives the order "eyes left," or "eyes right," it is frequently found that there is deficient movement, or a definite delay in deviation, of the eyes towards the side opposite to a frontal lesion. This symptom is not found in the case of tumours near the base of the frontal lobe, though it was not uncommon in lesions of the lateral aspect of the lobe.

Dr. JAMES COLLIER said he had listened with great interest to the papers and Dr. Gordon Holmes's comments. He agreed with the latter in regard to the syndrome of the optic atrophy on one side and optic neuritis on the other, which he had himself observed many times. It could only happen when there was a lesion far back in the orbital lobule, which either came frankly to the surface so as to press on the optic nerve, or so near to the surface as to give indications of local pressure.

He agreed that what Dr. Sachs said was true as to the frequent weakness of the face, and the absence of the opposite abdominal reflex. It was more particularly when the lesion lies towards the mesial aspect of the frontal lobe that most of these signs fail; and he thought that the sign Dr. Holmes brought forward, the delay and the difficulty with deviation of the eyes, was almost the only one he knew of which would help when the lesion was towards the mesial surface.

Dr. E. SACHS, in reply, said he agreed with Dr. Gordon Holmes when he said it was very important to consider the location of lesions within the frontal lobe, but there was not time when reading his paper to discuss this question. He agreed that the lesion must be at the base of the frontal lobe to produce the symptom which Kennedy described, but in many cases in which the lesion lay near the base of the frontal lobe and impinged on the optic nerve homolateral optic atrophy and contralateral papillœdema were not observed.

Another point he would like to make was, that there were a number of instances in which the lesion was along the longitudinal sinus, near the falx.

It was in that region that one would expect a lesion to cause loss of the abdominal reflex on the opposite side, without weakness of the face, since the latter was due to pressure on the lower portion of the central fissure. Yet there were instances in which the abdominal reflexes were equal in a lesion lying near the longitudinal sinus and yet a contralateral facial weakness.

The other sign mentioned by Dr. Gordon Holmes, namely, weakness of conjugate deviation of the eyes, he had not noted; but he had seen one case with slight nystagmus.

NUCLEAR OPHTHALMOPLEGIA, WITH ESPECIAL REFERENCE TO RETRACTION OF THE LIDS AND PTOSIS AND TO LESIONS OF THE POSTERIOR COMMISSURE.

BY JAMES COLLIER, M.D.
(*London.*)

THE clinical features which have been held to characterize ophthalmoplegia due to lesions of the oculomotor nuclei have always presented certain difficulties in bringing into line the well-known anatomical and physiological facts. While the oculomotor nerves are known only to gather their fibres from the nuclei of one side, yet a unilateral lesion of any part of the oculomotor cell mass does not usually, in the human subject, produce anything comparable to a simple paralysis, partial or complete, of its corresponding peripheral nerve. Perhaps a more just statement is that such an event has occurred so seldom as to allow so high an authority as Gowers to write: "Limitation of paralysis to one eye should not suggest nuclear disease. The characteristic feature of all nuclear disease is paralysis of the muscles of both eyes, internal or external, symmetrical or irregular" [1]. In the lower vertebrates which have not developed binocular vision, the nuclear mass of either side must be concerned simply with its corresponding oculomotor nerves, as are the fifth, seventh, ninth, tenth, eleventh and twelfth cranial nerve nuclei and the ventral horn nuclei of the spinal cord in man. And as there is no reason to presume a change of either the fundamental anatomical or physiological type in the transition from the lower to the highest vertebrate, it seems to me just to consider that the bilateral paralysis which is the common result of a unilateral lesion in the region of the oculomotor cell mass is essentially connected with the function of binocular vision, and that this bilateral paralysis is due not solely to the involvement of the cells of the nucleus but also to the coincident involvement of the paths of incitation which reach the oculomotor nuclei from the cerebrum, the function of which is strictly in terms of binocular vision and correlated movement of both eyes, and that the contralateral paralysis resulting from a unilateral lesion is always of this supranuclear type.

There does not seem to me to be any adequate reason for postulating

"supranuclear centres" situated in the brain-stem for the bilateral correlation of eye movements, since interruption of the down-coming path from the cerebrum would have a precisely similar effect as would the destruction of the hypothetical supranuclear centre. The pure varieties of supranuclear ophthalmoplegia, of which a clear example is reported here with the pathological findings, were clearly recognized by Gowers, for he writes of nuclear ophthalmoplegia that "certain forms may be due to disease of the corpora quadrigemina which does not penetrate the nuclei" [2]. He does not further comment upon this highly important statement of fact, but he obviously formulates the existence of a total external ophthalmoplegia from a lesion confined to the upper quadrigeminal region which leaves the oculomotor nuclei intact. Subsequent writers seem to have paid little attention to the results of supranuclear lesions.

There appear to be four possible modes in which lesions of the brain-stem can produce ophthalmoplegia: (1) By interrupting only the supranuclear path by which incitations descend from the cerebrum to the oculomotor nuclei, as in lesions situated at the junction of the thalamus with the superior colliculus, or when a lesion involves the posterior commissure, which is certainly an important decussation of the supranuclear path, since in the case recorded below a lesion of one-half of the posterior commissure caused complete loss of upward and downward movements of both eyes; and also when Meynert's decussation is involved. (2) By involving the cells of the oculomotor nuclei alone, as in chronic progressive neuronic degenerations, akin in nature perhaps to progressive muscular atrophy, and which have borne the names of Westphal and Siemerling, and also the acute neuronic affections which have been named peripheral neuritis of the eye muscles, of which diphtherial ophthalmoplegia, tetanus ophthalmoplegia, and the ophthalmoplegia met with in polyneuritis and in botulism are good examples. I think that the ocular paralysis of poliomyelitis should be placed in this group, since, like the facial paralysis in this disease, it seems invariably to recover. And I would class here also the ophthalmoplegia of myasthenia. When the affection is unilateral the resulting paralysis is indistinguishable from that produced by a partial or total lesion of the peripheral ocular nerves, and when bilateral and severe it may come to closely resemble the paralysis produced by the supranuclear lesion. I have seen strictly unilateral paralysis due to all the causes above mentioned in this group, but the bilateral cases are the rule. In myasthenia, for example, I have seen very considerable paralysis confined to one external

rectus precede the development of typical signs of this disease by many months, and in another case total unilateral palsy of the larynx precede the general signs of the disease by eighteen months. (3) By involving the intramedullary portion of the peripheral oculomotor nerve. And (4) by co-involving in a gross lesion any combination of the supranuclear path, nuclear cells and intramedullary peripheral nerve.

The common result of a unilateral lesion in the region of the fasciculus teres involving the sixth nucleus will serve to illustrate the above grouping. Most often one sees a paralysis of conjugate movements to the same side; this occurs when the lesion is just above or involves the head of the sixth nucleus where the cerebral path comes into the nucleus, and where also part of this cerebral path, either direct or mediate, ascends by way of the longitudinal bundles to the nucleus of the third nerve of the opposite side. Frequently with this same weakness of conjugate lateral movement to the same side there is a major paralysis of the external rectus. This happens, I submit, when there is implication of the bulk of the nucleus or an involvement of the sixth nerve itself in its intramedullary course, in addition to the supranuclear lesion. More rarely, a partial or complete paralysis of the sixth nerve results, and this, I suggest, occurs when a lesion encroaches upon the sixth nucleus at its lower pole and so causes no supranuclear paralysis, or when it involves the intramedullary part of the sixth nerve alone. This variability in the results of a lesion of the sixth nucleus gave rise, some years ago, to dogmatic and very contradictory statements, some authorities teaching that paralysis of lateral conjugate movements always resulted, and other authorities holding that simple paralysis of the external rectus occurred. Actually both statements were correct, the nature of the result being dependent upon the local relation of the lesion to the nucleus and its connections, while a blending of these results is common.

Attention is called in the following remarks to *retraction of the eyelids* occurring as an isolated phenomenon, or in connection with ophthalmoplegia, from lesions of the upper brain-stem in the region of the posterior commissure; this condition is a corresponding opposite of the sleepy lids or the ptosis so commonly seen with lesions in this same region, and two cases are reported in which these "corresponding opposites" presented side by side in the two eyes. These phenomena are obviously due to interference with different parts of that physiological mechanism which has to do with the raised lid of attention and the waking state, and the drooping lid of inattention and the sleeping state.

Surprisingly little attention seems to have been paid to this important clinical sign of retraction, since it is by no means a rare event, while ptosis has been one of the sign-manuals of quadrigeminal and sympathetic lesions since the days of Nothnagel. Gowers, however, did record it, for in dealing with nuclear ophthalmoplegia he writes: "The levators, however, seldom become completely paralysed and may be unaffected. The aspect of the patients is peculiar: when there is partial ptosis, this gives them a sleepy expression, and in total palsy without ptosis a staring look results" [3].

FIG. 1.—Extreme bilateral "tucked" lid in a patient aged 50 years, suffering from tabes and completely blind from optic atrophy, contrasting markedly with the partial bilateral ptosis so often met with in tabes. The external ocular movements were normal.

The object of this communication is to suggest:—

(1) That while it is usual with lesions of the mesencephalon in the region of the posterior commissure of the mid-brain to meet with partial bilateral ptosis of the so-called "sympathetic" type, often associated with small pupils and sometimes with complete loss of upward movements of the eyes; yet sometimes with lesions in the same region one may meet with a corresponding opposite, in that the lids are unduly retracted or tucked back and that the pupil may be large, and that retracted lids may be the sole sign of a lesion in this region.

(2) That the lesion responsible for the "tucked lids" and large pupils is situated farther forwards than is the lesion productive of ptosis and small pupil, and that the phenomenon of tucked lids may be seen when the lesion does not come farther back than the posterior limit of the posterior commissure. When such a lesion extends and encroaches farther back in this region of the brain-stem, the retracted lids fall and give place to the more usual ptosis, and the large pupils become small and may lose the light reaction.

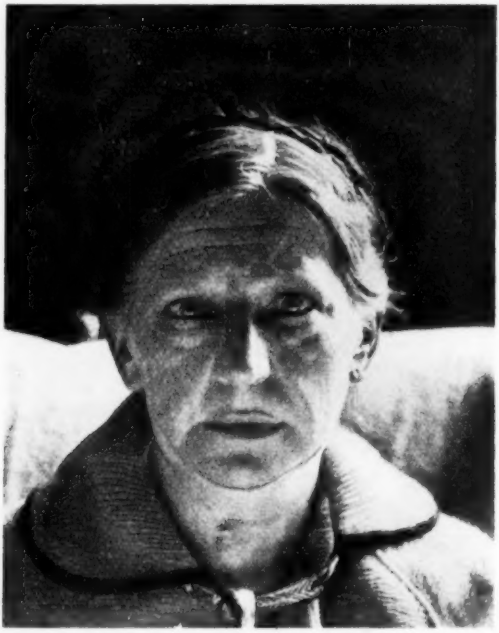

FIG. 2.—Congenital "tucked" lids, more marked upon the left side, comparable as a "corresponding opposite" with congenital ptosis. From a patient aged 52 years, in whom the retraction of left lid was first noticed within a short time of her birth. The ocular movements were normal.

(3) That in the majority of the clinical conditions in which ptosis and small pupils are well-known features, there may be observed instances of the "corresponding opposite" of retracted lids, sometimes with large pupils which react to light, sometimes with small pupils which do not react. Thus I have a case of congenital tucked lid corresponding with congenital ptosis (fig. 2); a blind tabetic with intense

retraction of the lids and no other ophthalmoplegic sign except reflex iridoplegia (fig. 1); and several other cases of tabes showing this sign, though ptosis is the common event in this disease. Further, I have cases of disseminate sclerosis with tucked lids in about the same numbers as present ptosis, and many examples of vascular, degenerative, neoplastic and encephalitic lesions of the upper brain-stem which have shown this sign. Conversely, I have seen a few cases of Parkinsonism which have presented ptosis instead of the almost constant retraction of the lids seen in this disease. There is under my care at the present moment, in St. George's Hospital, a girl with recent and somewhat severe Graves' disease with marked exophthalmos, but with marked ptosis instead of the retraction of the lids usual in Graves' disease. The clinical association of Graves' disease with ophthalmoplegia of the nuclear type, and also with myasthenia gravis, has long been known. Possibly all the ophthalmoplegia occurring in cases of exophthalmic goitre is of the nature of myasthenia, and this is a very plausible explanation of the case above cited. It may be here remarked that the ptosis of myasthenia has been known in rare instances to give place to persistent retraction of the lids.

(4) Further, to suggest that the ophthalmoplegias which have been commonly ascribed to lesion of the oculomotor nuclei, that is, loss of upward movement, of downward movement, of lateral movement of both eyes, and loss of convergence, respectively or combinedly, which were so well described both clinically and pathologically by Alexander Bruce, as coming on one after the other in progressive lesions involving the upper brain-stem from above downwards, are not all of them due to a lesion of the oculomotor nuclei at all, but that external ophthalmoplegia of this order can result from a lesion which does not extend lower than the level of the posterior commissure, and which isolates the oculomotor nuclei from down-coming incitations from the cerebrum, while the oculomotor nuclei are then intact. The clinical points which may serve to distinguish ophthalmoplegia of this supranuclear origin from that due to a nuclear lesion are tucked lids with unvarying parallelism and therefore no diplopia, contrasted with loss of parallelism, diplopia, ptosis and internal ophthalmoplegia in the nuclear lesions. In other words, regularity is characteristic of the supranuclear lesion and irregularity of the nuclear lesion.

My interest in the association of retraction of the eyelids with ophthalmoplegia was aroused many years ago by a patient in whom a total external ophthalmoplegia of long standing, and presumably due to

a vascular lesion, was associated from the time of its commencement with intense and unvarying retraction of the eyelids. I referred this case to the ophthalmic surgeons at St. George's Hospital for an opinion, with the result that within a few days they sent me three other cases of so-called nuclear ophthalmoplegia in which the same retraction of both lids was present. These were chronic cases with severe and unvarying retraction of both eyelids. In one of them the external ocular paralysis was complete, and in the other two it involved the upward and downward movements only. During subsequent years I have taken especial interest in the occurrence of retraction of the lids with lesions of the mesencephalon, with the result that I have ventured to bring forward these suggestions. The references which I have found to this subject in the literature are not numerous, and do not contain the proposition that retraction of the lids and ptosis are important localizing signs of lesions of the mesencephalon, and due to the involvement of two different mechanisms concerned with the position of the lids in the waking and in the sleeping states. Nor, with the exception of the single remark of Gowers above referred to, has the conception been hitherto formulated that complete or partial external ophthalmoplegia may occur from a lesion situated above the oculomotor nuclei which entirely spares them.

The following three cases, in which retraction of the eyelids was a prominent clinical feature, have an important bearing upon this subject:—

Case 1.—This case, for which I am indebted to my colleague, Dr. Feiling, was that of a woman, aged 49, with a blood-pressure of 200/145, and with a positive Wassermann reaction, who had never had a day's illness until she fainted at supper one evening, and, on recovering consciousness an hour later, found that she had right hemiplegia and aphasia. On admission to St. George's Hospital two days later, she had completely recovered speech, but presented right hemiplegia and hemianæsthesia. There was extreme retraction of both upper eyelids. No movement of either eye was possible upwards, downwards and to the right, and convergence was lost. Conjugate movement to the left was perfect. The axes were parallel; there was no diplopia, and the eyes at rest looked straight forwards. The pupils were small and equal and did not react to light. This patient remained intelligent and easy to examine for ten days. Subsequently she became exceedingly drowsy and died.

The necropsy showed a circumscribed capsulo-thalamic hæmorrhage on the left side, which extended downwards only just as far as the limits of the posterior commissure on the left side, just touching the anterior limit of the superior colliculus on that side. It completely involved the posterior commissure on the left side, but did not reach the middle line. It did not touch the red nucleus, and did not involve any structure below the opening of the

aqueduct, leaving therefore the oculomotor nuclei intact. In a section 3 mm. behind the anterior limit of the posterior commissure there was no trace of any lesion (fig. 3).

The important deductions which I have made from this case are: That a lesion not extending below the level of the posterior and not reaching the middle line, can produce intense and lasting retraction of both eyelids, together with a severe ophthalmoplegia of the nuclear type though the oculomotor nuclei are intact. This lesion must have completely divided all paths coming from above into the superior

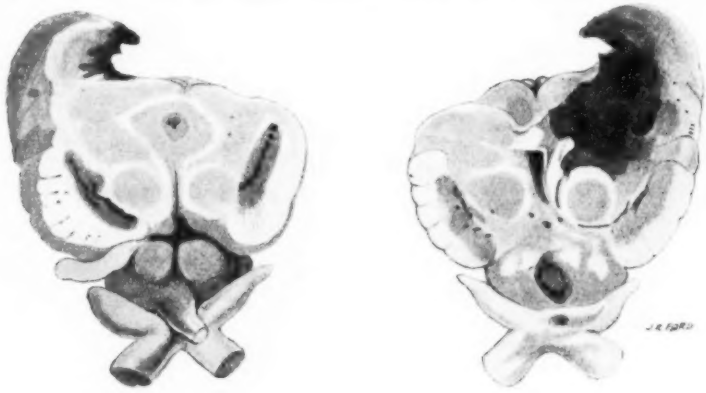

FIG 3 (*from Case* 1).—A unilateral lesion involving the left half of the posterior commissure and not extending backwards farther than the limits of the posterior commissure. The front view and back view of a slice 4 mm. thick cut in the plane of the optic tract. The section is slightly oblique. The strictly unilateral lesion at the level of the posterior limit of the third ventricle is well seen. It completely involves the left half of the posterior commissure, but hardly touches the left superior quadrigeminal body and leaves the grey matter around the aqueduct intact.

colliculus on the left side, as well as those entering the posterior commissure from the left side, and those crossing in the posterior commissure to the left side. It could not have involved any down-coming path on the right side unless this path crossed in the posterior commissure. Since in this case lateral conjugate movements to the left were perfect, t seems probable that the down-coming paths from the cerebrum for upward movement, downward movement and convergence cross in the posterior commissure, while those for lateral conjugate movement are situated more laterally and cross lower down.

Case 2.—This was a man, aged 69, with arterio-sclerosis, who was seized with giddiness and loss of consciousness for a few moments, and thereafter found that his left arm and leg were powerless, and that his left eyelid drooped.

The leg and arm recovered in a few days. I examined him a few hours after the seizure; there was complete external ophthalmoplegia and intense retraction of the left upper eyelid, with a moderate-sized left pupil which reacted to light. There was marked ptosis of the right lid, with a small right pupil which did not react to light. The contrast between the lids, out of sight on the left side and half dropped on the right side, was very striking, as was also the contrast between the large and active pupil and the small and non-reacting pupil. I submit that this patient had a lesion in the region of the posterior commissure on both sides of the middle line which involved all the down-coming paths for ocular movement, so causing a total external ocular palsy without diplopia. This lesion caused the retraction of the left lid, and as it extended farther back on the right side it involved the anterior part of the oculomotor nucleus, and caused the ptosis and non-reacting pupil on the left side. The complete external ophthalmoplegia was here of supranuclear origin. This patient made considerable improvement, doubtless owing to his lesion narrowing from collateral blood-supply, with the amazing result that the right pupil became larger and again reacted to light, and the right ptosis lessened day by day and gave place to a retraction of the right lid as extreme as that on the left side.

This case suggests that the lesion responsible for retraction is situated farther forwards than that which causes ptosis, and that the mechanisms for retraction and ptosis are strictly unilateral as regards the mesencephalon and the eye, since the two conditions may co-exist side by side.

Case 3.—This was a woman, aged 56, with arterio-sclerosis, who had had two attacks of hemiplegia, separated by an interval of six months. After the second attack she complained of mistiness of vision, and that the left eyelid had dropped. On examination she had a very slight right hemiplegia. There was complete loss of upward and downward movements of both eyes and of convergence, while the lateral conjugate movements to either side were perfect. The upper lid on the right side was markedly retracted, and the pupil was of moderate size and reacted to light. The left eyelid was half dropped, and the left pupil did not react to light. This condition remained the same so long as this patient was under observation.

This case shows that the mechanisms concerned with retraction of the lid and with ptosis may be separately and unilaterally affected, and that these physical signs may co-exist in the same patient when a local lesion of the upper mesencephalon is bilateral and oblique, or when such a lesion extends farther back upon one side than upon the other. I submit that the lesion in this case was in the region of the posterior commissure on either side of the middle line, so producing the complete

loss of upward and downward movements and of convergence by causing a supranuclear lesion, and not extending far laterally, so leaving intact the descending paths which subserve lateral conjugate movements.

REFERENCES.

[1] Gowers, "Diseases of the Nervous System," Second Edition, **2**, 194.
[2] *Ibid.*
[3] *Ibid.*, 159.

DISCUSSION.

Professor Edwin Bramwell said that Dr. Collier's reference to myasthenia gravis recalled a case of this disease which he had had under observation for eighteen years, in which there was complete bilateral external ophthalmoplegia, apart from some slight power of convergence, together with very pronounced retraction of both upper lids. There were no symptoms of hyperthyroidism in this case. A further point of interest, with no direct bearing, however, on the point under discussion, was that after the typical symptoms of the disease had persisted for some two years, the patient appeared to make a complete recovery and was able to carry out arduous physical work for a period of eleven years, when a relapse occurred associated with the ophthalmoplegia above referred to.

Dr. Cadwalader said he had been much interested in Dr. Collier's remarks on the different forms of ocular palsy, as he had recently had the opportunity of studying a case of complete external ophthalmoplegia with preservation of the pupillary reflexes, a case which he thought belonged to the type described by Siemerling. This patient developed ptosis first, and afterwards a complete external ophthalmoplegia when 38 years of age, but the pupillary reflexes for light and accommodation remained normal. She was healthy in all other respects, presented no signs of other nervous disease and came of a healthy family. She died at the age of 74. The study of the brain was not yet completed, but he could say that each third nucleus was severely affected though not completely destroyed, as some cells remained.

Dr. Collier had referred to the supranuclear type of ophthalmoplegia. He had seen several such cases clinically, but had not had the opportunity of examining one post mortem. During the past year he had seen, however, with his chief, Dr. Spiller, two cases in which a painstaking examination had led Dr. Spiller to the conclusion that a supranuclear lesion in the subthalamic region had caused a sympathetic type of palsy, probably similar to what Dr. Collier had described.

There is a form of retraction of the lids which might be termed a widening of the palpebral fissures; it is often seen in cases of progressive lenticular degeneration, and in some cases of the post-encephalitic Parkinsonian syndrome. He thought this condition might be similar to what Dr. Collier had spoken of as retraction of the lids, and he wished to throw out the suggestion that it might have some relation to involvement of sympathetic fibres in the subthalamic region.

Dr. JAMES COLLIER, in reply, thanked Professor Bramwell for his remarks on myasthenia gravis. He had intended to include a similar observation in his paper.

With regard to Dr. Cadwalader's remarks, there is great difficulty in distinguishing between a pure supranuclear lesion and a pure nuclear lesion; in most cases, however, both lesions are present, for he did not think that fibres coming from above terminated abruptly in any nuclear structure. Therefore one was dealing, in the case of the gross nuclear lesions, with a mixture of supranuclear and nuclear affections.

He was interested to hear that Dr. Cadwalader had seen retraction in purely degenerative lesions, and also such a complete and lasting ophthalmoplegia in a purely degenerative lesion. It was well known that in myasthenia gravis ophthalmoplegia might become complete and remain so until the end of life. In the first case he described, which had marked retraction, there was a subthalamic lesion.

THE MECHANISM OF CICATRICIAL CONTRACTION IN THE BRAIN.

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REPAIR of brain wounds has been studied from one aspect or another by numerous investigators. The principles and cytological changes involved have never been completely worked out. During the past five years I have worked upon different aspects of this problem. After studying meningo.cerebral adhesions [10] it became apparent that a complete understanding of the subject depended upon further knowledge of the details of the neuroglia reaction involved. This was undertaken with Dr. Del Rio-Hortega [4], whose previous work marks an epoch in the understanding of the interstitial cells of the central nervous system. In these earlier studies it became evident that the presence of connective tissue in a wound was at times prevented, and that such a wound presented a striking contrast to other brain wounds and to wound healing as it appears elsewhere in the body. This difference was investigated with Dr. Buckley [14].

It is possible now to discuss the principles which underlie the process of wound healing in the brain, to outline the factors involved in cicatricial contraction, and to point out certain misconceptions which have been responsible for many of the hitherto proposed cranioplastic operations for Jacksonian epilepsy.

As extended bibliographic references can be found in the above-cited publications only a few will be added here.

STRUCTURAL FRAMEWORK.

The mechanism for support in the central nervous system is quite different from that in other organs. The pia mater serves as a delicate capsule dipping into all the crevasses, but there are no connective tissue septa within it, as in other organs. In place of septa the only continuous structure, except for nerve fibres, is the vascular tree which ramifies in the pia mater everywhere and penetrates perpendicularly into the nervous tissue.

The structural connection between vessels and nervous tissue is by

means of the neuroglia astrocytes. That these cells serve a supportive function is a very old suggestion. Every astrocyte has at least one, and usually many, perivascular attachments or sucker-feet (Cajal [2]). The astrocytes of the normal grey matter are, in general, protoplasmic, which is to say that they contain no fibres. Such strain as they are capable of supporting must be slight indeed, but the vascular plexus of the grey matter is many times denser than elsewhere.

All other astrocytes contain fibres. These fibres pass into the cell body by one expansion and out of it along another. They are not normally divorced from the parent cell (as appears to be the case when Weigert stains are used) but apparently carry a thin coating of protoplasm about them. The perivascular expansions end upon or about a capillary or small vessel, and the fibre or fibres may spray out over the vessel wall like a lock of hair. Thus a glial fibre may pass from one perivascular attachment through the cell to another, as though capable of binding the two vessels together.

Everywhere in a zone beneath the pia mater the astrocytes are fibrous and are attached by their expansions to the under-surface of the pia, just as they are to the vessels. Even in the underlying grey matter pathological influences of various types result in the appearance of fibres within the normally protoplasmic astrocytes.

The nature of the actual connection between astrocyte and vessel (or pia mater) is still somewhat in doubt. The footplate, as Held and many others conceived it, was an irregular tile in a tubular mosaic which afforded an ectodermal barrier to all things mesodermal, including pia and vessel. Ingleby [8] held that fibres pass from the "podic" into the vessel wall; Cajal [2] was undecided whether the expansions actually touched the vessel or were separated from it by an enigmatic substance in the perivascular space.

Perhaps the best evidence, however, that the perivascular foot provides a hold of some sort capable of withstanding tension is the demonstration in this communication of the displacement of astrocytes, or at least of their expansions by traction exerted upon them through the vessels.

The octopus-like astrocytes, therefore, hold the manifold structures of the nervous system within their tentacles, and are attached to pia and vascular tree by specialized expansions. This is the supporting framework of the adult nervous system,[1] rather than a problematic or imaginary syncytium [13].

[1] In the more primitive forms of nervous system support is evidently provided by ependymal glia. These cells possess two expansions, one applied to the medullary canal and the other to the external limiting membrane. With the invasion of the central nervous system by the vascular tree blood-vessel feet are gradually substituted for subpial terminations and ependymal footplates.

For the sake of convenience in the discussion which follows, it will be referred to as the *vaso-astral framework*.

Meningo-Cerebral Adhesion.

Unless there is abnormally high intracrannial pressure, the brain is seen to pulsate beneath the dura when a craniotomy is performed. This pulsatile movement takes place partly in the subdural space, and it should be recognized that this is an actual, not merely a potential space, and that it contains normally a thin layer of yellowish fluid [11]. The subdural space then may be likened to the pleural, pericardial and peritoneal spaces. Incision or removal of dura mater without injury to arachnoidea results in regeneration of dura with little or no adhesion between the two membranes [9] [10]. Injury to pia-arachnoid results in the formation of an adhesion.

This difference of reaction is not necessarily evidence of a difference in the origin of the pachy- and lepto-meninges, however. Injury to pia-arachnoid breaks the barrier formed by avascular arachnoid and necessarily removes the protective covering of the nervous system. Such a break calls forth an energetic connective tissue response, whether the nervous tissue is exposed in the central or peripheral system, as though nervous tissue were indeed a foreign body [15].

The amount of adhesion varies directly with the amount of injured cerebral tissue which is left behind. If a stab wound be made, as by the introduction of a blunt brain needle without removal of cerebral tissue, a connective tissue adhesion forms of such tensile strength that, when at autopsy the dura is elevated, a core is withdrawn from the wound tract by the firmly attached dura [10]. If the *injured tissue be removed* by using a hollow needle to ream out a cylinder of brain *no connective tissue core* is formed and the surface adhesion is only a slight one [14]. Blood-clot forms in both instances, but it is evident that the presence of injured cerebral tissue is responsible for the energy of the superficial fibroblastic growth.

By the use of Cajal's gold chloride-sublimate method, the astrocytes are stained selectively.[1] They are increased in number, are fibrous, and, where pia mater is not destroyed, maintain the application of their sucker feet to its under-surface for the most part. At certain points, as illustrated in fig. 1, astrocyte expansions may be seen to pass right up through the pia and into scar beyond. These expansions may be traced

[1] The constructive reaction of the nervous tissue to brain wounds is carried on by astrocytes only. Oligodendroglia seems to play no active rôle in the formation of the cicatrix. Microglia is involved only as a source for the formation of compound granular corpuscles which remove the products of destruction.

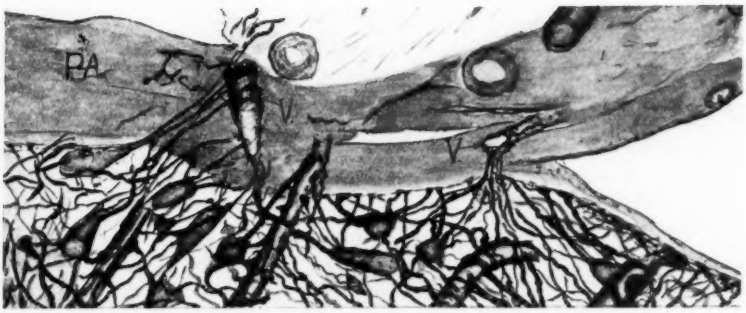

FIG. 1.—Meningeal adhesion near stab wound which was made ninety-two days previously in brain of dog. The blood-vessels (V) have been pulled into the scar and have drawn the astrocyte expansions through the pia-arachnoid (P-A).

FIG. 2.—Photomicrograph of part of the field from which fig. 2 was drawn. The pia-arachnoid is unstained. Astrocyte expansions may be seen passing through this membrane. Cajal's gold chloride sublimate stain (G.C.S.). × 320.

to blood-vessels in the overlying scar. That the expansions do pass upward through pia may be seen also in the photograph (fig. 2) of the same field, although it is not possible to focus the vessels to which the expansions are attached upon the photographic plate along with

FIG. 3.—Superficial pial adhesion near brain injury. The pia-arachnoid is unstained. Note hypertrophy of zonal glia and alignment of astrocytes below toward the pul' G.C.S. × 184.

the major part of the expansions themselves. The pia and connective tissue of the scar are unstained by gold chloride, the astrocytes being exclusively impregnated.

It does not seem likely that such expansions would grow out through

connective tissue to seek a vessel, when it is a well recognized biological characteristic of these cells to throw up a barrier against such tissue by means of their perivascular and subpial footplates. The vessels referred to are continuous from brain to dura and scar, by virtue of the adhesion anastomosis. Within the brain such vessels are naturally surrounded by perivascular expansions. On the outside these vessels are incorporated in a mass of new-formed connective tissue. It is, of course, characteristic of such connective tissue scars to contract. It may be expected,

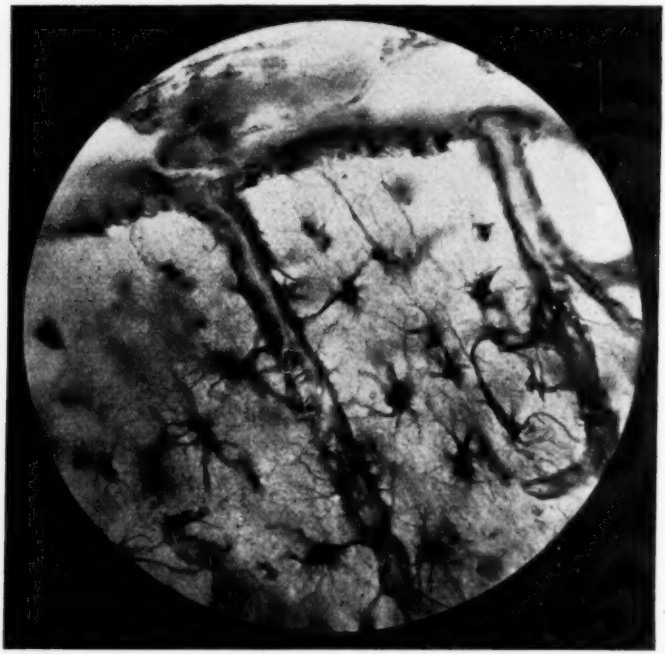

FIG. 4.—Fibrous astrocytes about vessels entering cortex; normal. G.C.S. × 326.

therefore, that a pull should be exerted upon the vessels which seem thus to be drawn partially out of the brain through the pia and into the overlying scar.

Perivascular attachments are evidently capable of withstanding this pull. Thus, the fibrous expansions are drawn out and doubtless elongate and hypertrophy. Whether or not the cell body and nucleus are displaced by the pull is difficult to determine with certainty. In other types of gliosis it is evident that astrocyte expansions are capable

of hypertrophy and elongation as shown by their marked tortuosity, the cell body and expansion attachment under those conditions being fixed points.

Such mechanical traction may be exerted directly upon the pia mater by an overlying scar at points where there is no evidence of a brain laceration. This is illustrated in fig. 3 where the unstained leptomeninges and vessels have drawn the ridge of a convolution to one side. It can be seen that there is secondary hypertrophy of the zonal glia immediately beneath the pia and that the underlying astrocytes point with many of their larger expansions in the direction of the pull. The traction in this instance is evidently on the pia mater itself without

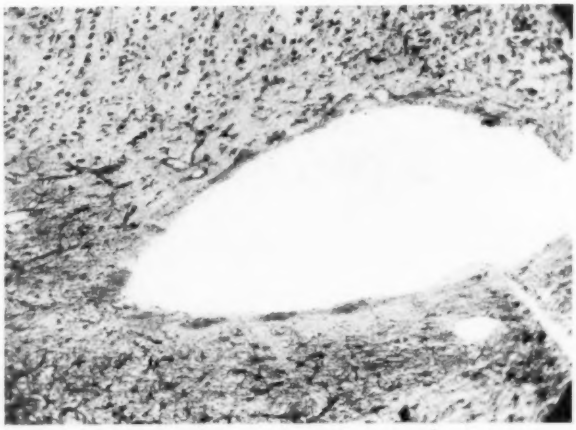

FIG. 5.—Hollow tract made by brain-stab with needle six months previously (dog). No connective tissue. Slight gliosis only. G.C.S. × 76.

actual laceration of the brain at this point. It seems unlikely the arrangement of astrocytes can be due to anything but the influence of traction upon the pia mater, the maximum effect being on the zonal glia.

Beneath a decompression wound, which is similar to that in fig. 3 in every way except that no adhesion occurred, the arrangement of the superficial astrocytes is seen to be quite normal (fig. 4). There is no hypertrophy of the zonal glia beneath the pia mater and the larger astrocyte expansions assume their normal orientation perpendicular to entering vessel or to pia. With no hypertrophy the vessels themselves are unstained, being outlined by perivascular feet and glial fibres.

If traction upon pia and upon vessels at the surface of the brain

exerts an influence upon the adjacent astrocytes and even draws their expansions out of their natural environment, it seems likely *a priori* that a similar process involves the vaso-astral framework when the cicatrix is situated within the brain itself.

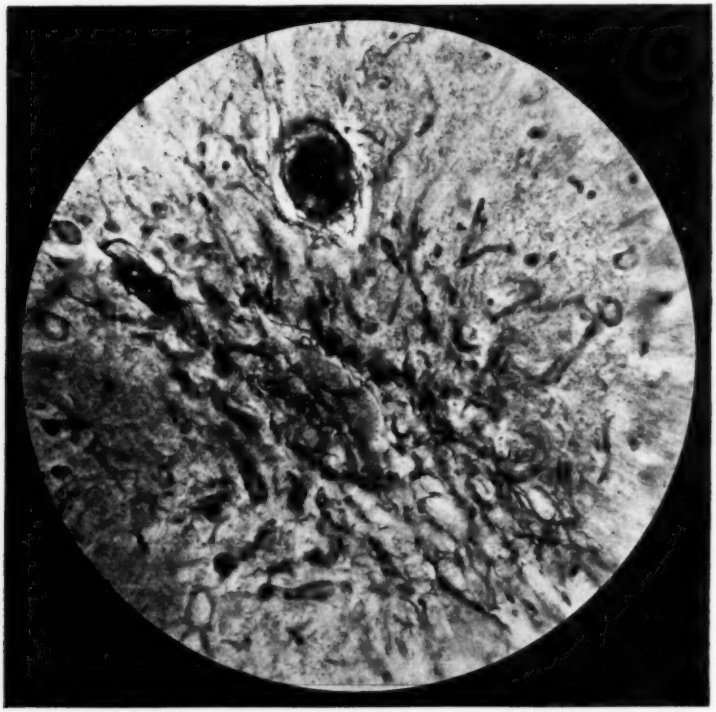

FIG. 6.—New-formed collagen fibres in small brain-stab of nineteen days' duration (rabbit). Silver carbonate connective tissue stain. × 347.

BRAIN WOUNDS WITH NEITHER CICATRIX NOR CONTRACTION.

Removal of the injured cerebral tissue naturally reduces the number of compound granular corpuscles to a minimum. It reduces the amount of gliosis also to a small amount in the grey matter, and reduces it in the white matter to a still greater extent. In spite of the fact that the wound fills with blood-clot, no connective titsue core is formed except for occasional mural wisps of connective tissue [14]. Thus a gaping hcle is left in the brain (fig. 5). For such a result the asepsis must be

perfect, of course, as infection greatly increases both the mesodermal and ectodermal response.

Thus it is possible to produce brain wounds which leave only a small amount of superficial adhesion, as mentioned above, and result in nothing but a fluid-filled hole in the brain itself. The pre-requisite for such a result is the removal of all injured tissue.

Contracting Cerebral Cicatrix.

On the other hand, after the retention of injured cerebral tissue, even due to so seemingly innocent a procedure as inserting a blunt needle which does not remove the tissue encountered, a different and more energetic response results. Phagocytosis[1] goes forward. A connective

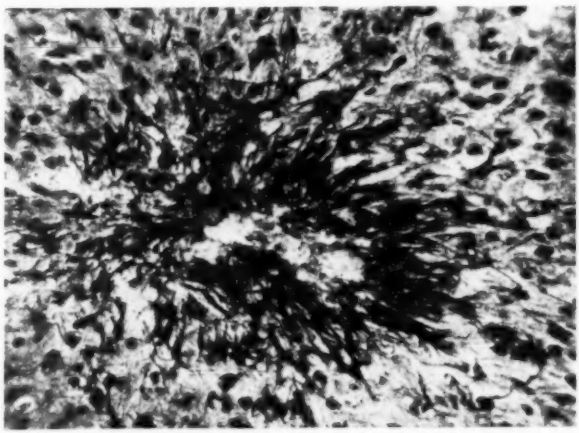

Fig. 7.—Closed small stab-wound made in brain of rabbit with closed needle eleven days previously. There is connective tissue at centre which is unstained. G.C.S. × 180.

tissue core is formed by rapidly growing fibroblasts. Before the end of the third week new-formed collagen fibres (reticulin) are present in the core itself as well as on the vessels of the wound (fig. 6).

The nearby neuroglia astrocytes, except those destroyed by direct trauma, undergo rapid division and enlargement and become fibrous, even though they may have been of the protoplasmic type without

[1] Phagocytosis is carried out by compound granular corpuscles or Gitterzellen. The transformation of microglia into these cells is easy to see about a recent brain wound. That the compound granular corpuscles may also develop from leucocytes and adventitial cells is discussed elsewhere [12], though they probably are not derived from neuroglia astrocytes [4].

fibres before the wound was made. If the wound be a small one the astrocyte expansions soon take on a concentric arrangement like spokes of a wheel (fig. 7). Their large expansions are directed toward or away from the connective tissue core as though they were influenced by contraction there, just as the astrocytes described above were influenced by the superficial adhesion (fig. 3).

In fig. 8 unaltered protoplasmic astrocytes are shown in the cerebral cortex of a dog at a distance from the wound. Fig. 9 shows the astrocytes of the cortex near the wound in the same case. The magnification of the two figures is the same, so that they illustrate the enlargement and the change to fibrous type. The fibres are not differentially

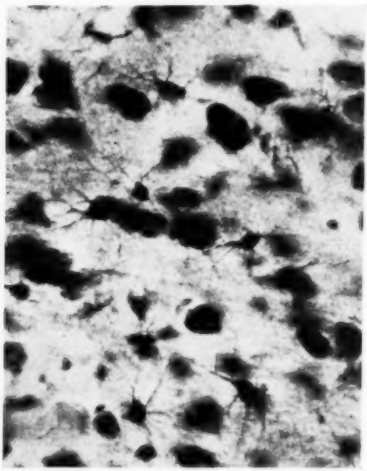

FIG. 8.—Protoplasmic astrocytes in cerebral cortex of dog; normal. G.C.S. × 331.

stained, but the shape of the expansions indicates that they contain fibres. Fig. 10 is from the same case and shows astrocytes near the wound, which point in the direction of the wound with their fibres. Thus, gliosis in response to a wound may occur without evidence of contraction as in fig. 9. This is probably due to some interference with circulation. In a zone nearer the connective tissue core the orientation of the hypertrophied astrocytes is altered (fig. 10), presumably by contraction of that core.

The question naturally arises as to whether this arrangement of neuroglia expansions really indicates a widespread traction upon the brain vessels, or whether some other influence causes such an alignment.

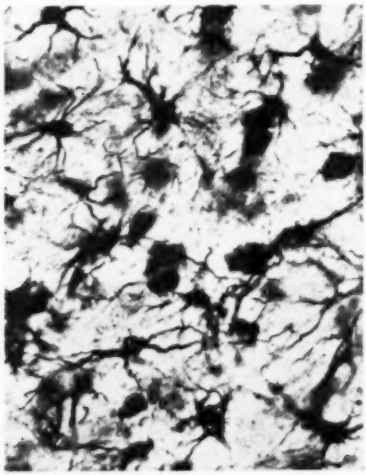

FIG. 9.—Hypertrophied astrocytes in cerebral cortex; same case as fig. 8, neighbourhood of wound. G.C.S. × 331.

As was pointed out above, about the gaping tracts made by open cannulas with removal of cerebral tissue, the astrocyte expansions bear no particular relation to the tract, or else are arranged in a tangential manner suggesting that the opening may progressively enlarge. There is no

FIG. 10.—Hypertrophied astrocytes showing orientation toward wound which contained connective tissue. Same case as fig. 9 but nearer wound. G.C.S. × 331.

orientation toward a wound which contains no connective tissue core. It would seem that either the connective tissue or the destroyed cerebral tissue plays the important rôle.

The radial arrangement can hardly be explained as a chemotactic influence exerted upon the astrocytes by either connective tissue or the products of destruction, for the large expansions starting in the cell body point away from the wound as well as toward it. The radiating expansions are the larger branches of any particular astrocyte, and are also the expansions attached to vessels (fig. 11). The smaller expansions

FIG. 11.—Hypertrophy of perivascular expansions of astrocytes indicating direction of pull towards closed stab-wound of six weeks' standing (dog). G.C.S. × 260.

may show little tendency to such an arrangement. If then the orientation toward the scar is not due altogether to some type of bio-taxis it would seem that contraction of the connective tissue scar may well be a factor.

In addition to the new collagen which forms so rapidly in a closed brain wound (fig. 6), there is a very rich plexus of vessels which anastomose with the surrounding vessels of the brain [14], thus forming a direct connection with the vaso-astral framework proper to the brain. Just as connective tissue scars elsewhere in the body tend to contract, so contraction occurs in the brain. The resistance to such contraction must be comparatively slight because of the consistency of cerebral

tissue. There must result, therefore, traction upon the vessels of the brain itself by virtue of their anastomosis with the vascular plexus in the scar.

If a fish net, which is made up of cords arranged in little squares, be gathered up at one point, the sides of the squares come to radiate roughly toward and away from the gathered area. The vessels and connecting astrocytes may be likened to such a net. A small amount of traction upon vessels in a scar might well cause tension in and resultant hypertrophy of the perivascular glial expansions which are in line with the

FIG. 12.—Parallel astrocytes, result of pull from contracting wound. G.C.S. × 520.

pull without affecting the other expansions very much (figs. 11 and 12). This would affect those glial expansions which radiate away from as well as toward the wound, and these are in fact the ones which undergo hypertrophy.

In larger wounds with much brain destruction, and particularly in those where there is some degree of infection, the resultant gliosis and cicatricial contraction is many times increased (fig. 13). Instead of a rather slender core of connection tissue, there is widespread fibroplastic growth and a network of collagen fibres (fig. 14) is laid down so vigorous, dense and tangled that the contractile force might well be considerable.

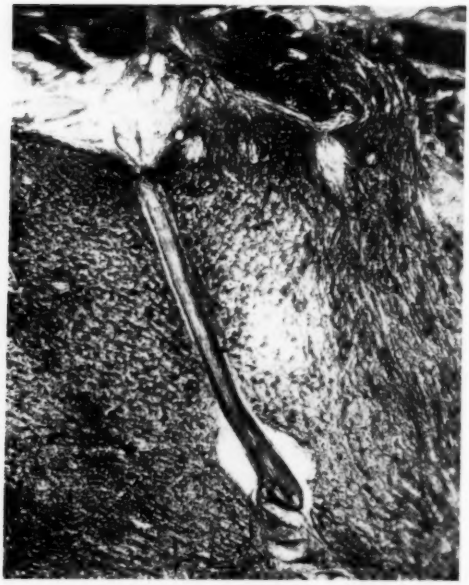

FIG. 13.—Brain scar, forty-eight days after gross wound of the brain. Adhesion above to muscle. Both collagen fibres and astrocytes are stained. Hortega silver carbonate astrocyte stain. S.C.A. × 55.

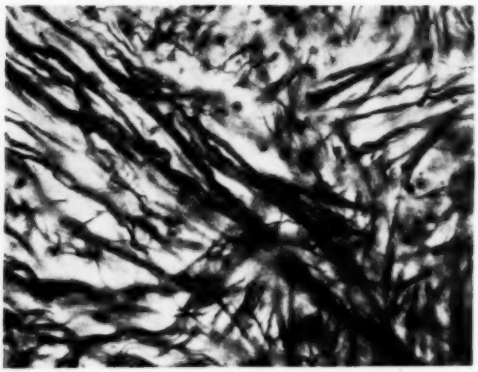

FIG. 14.—Collagen in brain-scar; same case and section as in fig. 13. S.C.A. × 340.

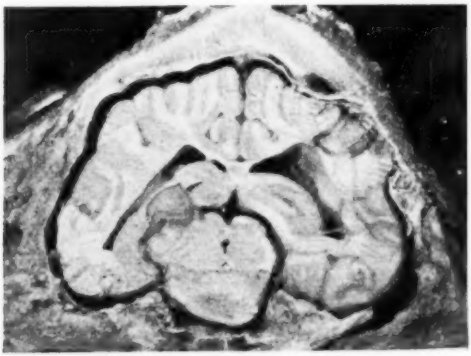

FIG. 15.—Brain of dog in skull and showing adhesion of the brain to muscle through the craniotomy. Wall of ventricle pulled toward wound. ⅔ life size.

FIG. 16.—Pneumogram of anterior horns of lateral ventricles to show wandering of ventricles toward the side of brain wound. (After Foerster.)

The surrounding gliosis is equally vigorous. In such wounds compound granular corpuscles are present long after the time when they would have disappeared about a small wound. Their continued presence sometimes suggests progressive cerebral destruction.

If such traction is exerted local movement of the brain is to be expected. This is, in fact, the invariable accompaniment of closed brain wounds. The cortex may be pulled down toward the connective tissue core, and the white matter, in the gross, can be seen to deviate toward the focus.

In experimental animals the brain at the site of the wound is pulled up through the operative bony defect by scar in the overlying muscle. That this is not due to simple brain œdema is testified to by the passive enlargement of the underlying ventricle (fig. 15), showing that the lateral wall is pulled away, not pushed out by the rest of the brain.

From the clinical side also we have evidence of a widespread pull upon the whole brain exerted by a brain wound. Foerster [7], in his encephalographic studies of patients with brain wounds, has noticed a "wandering" of the ventricles to the side of the lesion (fig. 16) which is substantiated by Wartenburg [16]. If it is borne in mind that in the brain there is only one continuous structure possessed of tensile strength, which is the vascular tree, and that connection between vessel and the brain itself is by means of the astrocyte expansions, it becomes evident that pull toward such a lesion is explained by the mechanism described above. The focus of this pull is a scar which, like connective tissue scars elsewhere in the body, contracts slowly but progressively over a long period of time. The consistency of the brain is such that it can offer but slight resistance to such a pull. The mechanism of cicatricial contraction explains the clinical observations of Foerster.[1]

Discussion and Summary.

The structural framework of the central nervous system, and particularly the brain, may be considered to be composed of pia mater, blood-vessels and neuroglia astrocytes. The vessels pass perpendicularly into the brain from every surface, carrying with them, at least for a distance, a pial sheath. The astrocytes by means of their perivascular expansions hold the small vessels and pia mater in a sort of spongy framework which is capable of withstanding strain when these cells are fibrous. It has been pointed out that astrocytes are fibrous everywhere beneath the

[1] Professor Foerster was kind enough to send me a number of pneumogram reproductions which illustrate the dislocation of the ventricles toward the site of brain injury. Such widespread cicatricial contraction must be a factor of not infrequent occurrence in clinical conditions, especially in cases of traumatic epilepsy.

pia as well as in the white matter. Although this is not a new conception it is emphasized here because of its great importance in the understanding of the mechanism of cicatrization.

For convenience the whole supportive structure might be called the *vaso-glial* framework, or better, inasmuch as oligodendroglia plays no primary rôle in it, the *vaso-astral framework*.

Meningo-cerebral adhesions form when the pia mater is injured and cerebral tissue exposed. An anastomosis is thus established between cerebral and meningeal vessels by way of the adhesion or scar. In such a scar are to be found astrocyte expansions attached to vessels well out in the connective tissue, while the astrocyte cell body remains beneath the pia. This is taken as evidence of superficial contraction of the cicatrix which pulls a vessel once beneath pia through that membrane into the scar, thus carrying with it the attached astrocyte expansions which evidently hypertrophy under tension.

In areas of pial adhesion where no break is visible in brain structure, there is marked hypertrophy of the subpial astrocyte expansions in the direction of the adhesive pull, while their other smaller expansions may radiate in all directions as usual.

Contraction of a connective tissue cicatrix within the brain seems to draw towards it the vaso-astral framework. Collagen fibres appear early in the tract and very many vessels. The many newly formed fibrous astrocytes point toward or away from the wound tract with their most robust expansions. These robust expansions have perivascular attachments and are apparently those which happen to be in line with the cicatricial pull. Thus, because the vessels in the scar anastomose freely with the surrounding cerebral vessels, the vaso-astral framework is pulled upon.

To bear out the probability that such is the underlying mechanism in cerebral cicatrization, there is found consistently gross evidence of distortion of the brain and movement of its landmarks toward the cicatrix. This may be extensive enough to pull the lateral wall of the lateral ventricle toward the scar, and even cause deflection of both ventricles toward that side according to the cases studied by Foerster.

Cerebral cicatrix can be largely avoided if injured cerebral tissue be removed completely, and the removal be not too superficial. There results then a gaping hole containing little or no connective tissue and surrounded by a minimum of gliosis. There is under such circumstances no radiation of the astrocyte fibres toward the tract, no evidence of contraction, no local increase of vessels and only slight superficial adhesion.

The difference in reaction to the two types of wound may perhaps be

due to the retention of destroyed cerebral tissue in the one and not in the other. This tissue calls forth most energetic phagocytic activity and rapid growth of fibroblasts, with the early appearance of collagen fibres and new vessels. If injured cerebral tissue be carefully removed, the tract is filled immediately with blood-clot which seems to be soon replaced by fluid.

Embolism or closure of a cerebral vessel from whatever cause may produce a fluid-filled space not infrequently. It does not give rise to the formation of much connective tissue and the gliosis is less robust.

Such holes do not follow tissue removal elsewhere in the body. The difference may be in part due to the fact that the brain is contained in a rigid box incapable of the collapse necessary to fill a dead space. Also it must be remembered that cerebrospinal fluid is present in the cranial cavity to fill that dead space, and eventually wash out the fibrin resulting from the blood-clot, provided macerated brain be not present also.

An understandiug of the mechanism of wound healing must have many applications to the procedures of neuro-surgery. One application will be mentioned. The cranioplastic operations which are designed to fill brain wounds with foreign material defeat their very purpose at the start, inasmuch as the implanted material produces a violent foreign body reaction. If they are viable, e.g., fat or fascia, the material is incorporated in a new and extensive adhesion as connective tissue grows rapidly on both sides.

In order to eliminate cicatricial contraction and provide for the formation of a fluid-filled space with a minimum of adhesion, injured cerebral tissue should be cleanly removed or the old scar excised, while the defect in the skull is closed, thus leaving a dead space filled with fluid.

It would seem that a contracting scar from brain injury must eventually destroy a larger portion of cerebral tissue than would be destroyed by the initial removal of an equal portion of brain. Also the slow contraction of such a scar, continuing as it does for years, must produce a constant irritation which may well be the starting point for a nervous discharge resulting in Jacksonian epilepsy. Clean excision of such a cicatrix should convert a contracting scar into a fluid-filled space and relieve the remainder of the brain from abnormal traction.

Finally, fibrous astrocytes serve a supportive function in the central nervous system, forming with the blood-vessels a vaso-astral framework. The mechanism of cicatrization in the brain is as follows : The vaso-astral framework, being caught in the mesh of a contracting connective tissue scar, is drawn toward the scar, exerting traction upon and causing distortion of the surrounding brain. The presence of macerated cerebral

tissue in a brain wound is the predisposing cause of the appearance of such connective tissue.

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DISCUSSION.

Dr. J. G. GREENFIELD said he had no criticism to make, and very few comments to offer on the paper, as this was absolutely new work, and work of a very valuable kind. He had been wondering whether Dr. Penfield's researches into the ultra-microscopic were directed towards a practical end, but now he saw that they had been. The work of Hortega on the neuroglia was of the greatest importance, and Dr. Penfield's work on scar wounds seemed to give an answer to other work which had suggested that the cause of adhesions of the brain to meninges after even slight damage to the pia arachnoid was due to the fact that the arachnoid and neuroglia were embryologically one tissue; that one was not neural and the other mesodermal, but both were derived from the neural crest. Dr. Penfield's work gave a more rational explanation, and was of the greatest value, not only as showing why the brain became adherent to a scar, but as affording a reasonable hope that in some cases it might not become so.

SUPRASELLAR ENDOTHELIOMATA.

BY GORDON HOLMES, M.D.

AND

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(*London.*)

THE tumours with which we are dealing here are not among the more common causes of compression of the intracranial portions of the optic nerves and the chiasma, but as we have met with six of the ten cases which form the subject of this paper during the past three years they cannot be very rare. They deserve attention particularly because they are accessible to surgical treatment and, as our experience shows, may be completely removed provided they have not attained too great a size before operation is undertaken. Their early diagnosis is consequently very important, and it is, we believe, possible in most cases if the clinical symptoms which they produce are clearly recognized.

The tumours in our ten cases were all typical endotheliomata; in a few psammoma bodies were found in the epithelial whorls, but these may appear in all slow-growing endotheliomata of arachnoidal origin.

Isolated instances of these suprasellar endotheliomata can be found in the literature, but as far as we are aware no critical study of their symptoms has yet been undertaken. Cushing [3] in his paper on dural endotheliomata, in 1922, mentions that in his series of eighty-five endotheliomata, eight examples occurred in this position, and adds that their clinical manifestations were very similar to those of the cranio-pharyngeal pouch tumours.

ORIGIN.

It has been established by Schmidt [5], and later by Cushing [3], that the meningeal endotheliomata arise, not in the dura mater to which they are so firmly attached, but in the villous processes of the arachnoid which, in their macroscopic form, are known as Pacchionian bodies, and attain their maximum development along the sagittal sinus. Le Gros Clark [1] has shown that as microscopic structures they are very widely distributed, particularly in the neighbourhood of the intradural blood-spaces, into which they project, their function being to transfer the cerebro-spinal fluid into the venous

system. Each process has a multicellular endothelial cap continuous with the endothelial lining of the venous channel into which it projects. Such intradural venous channels exist in the diaphragma sellæ, particularly at its periphery. It is therefore reasonable to suppose that the tumours with which we are dealing originate from the Pacchionian bodies of the circular sinus. In three of our specimens the point of attachment of the tumour can be seen to be situated at the periphery of the diaphragma sellæ.

They are consequently primarily intracranial, and must be distinguished from the endotheliomata that arise from the dural sheaths of the optic nerves and occasionally extend into the cranial cavity through the optic foramina; as Hudson [4] has shown, this backward extension of intra-orbital endotheliomata is not rare, but the symptoms which they then produce differ from those that characterize our group.

Morbid Anatomy.

As they appear when exposed at operation, some of these tumours are soft, reddish and somewhat vascular, and though clearly encapsulated and readily separable from the surrounding structures, tend to wrap round and obscure them. Others are more spherical and regular in shape, and have a thicker capsule, but even these tend in places to envelop the contiguous arteries, which come to lie in deep grooves so as to appear embedded in the tumour. This is naturally of great moment from the point of view of complete removal. In one specimen it is clear that the anterior cerebral artery would certainly have been torn in any attempt to shell out the tumour whole. In structure these tumours do not differ from other endotheliomata.

In two of our cases the tumours had attained such a size that they compressed the base of the brain, or perhaps one of the cerebral peduncles, sufficiently to produce a slight degree of hemiplegia. In one of these the compression of the inner aspect of one temporal lobe was responsible for the occurrence of epileptiform seizures of uncinate type. In another of our cases smell was defective.

Clinical Notes.

Case 1.—J. G., male, aged 41, first attended St. Thomas's Hospital, under Dr. H. G. Turney, in 1908, complaining of failure of vision in the left eye of six weeks' duration. The loss first began in the temporal field, and gradually extended over the centre. At the first examination there was temporal hemianopia in the left eye, with pallor of the disc; the right field was full and the disc normal.

Three months later the left eye was completely blind, whilst the temporal field of the right eye was contracted. Four months later the right disc had become pale and the temporal field further encroached upon. At this time a radiogram of the sella turcica showed nothing abnormal.

Eighteen months after the first defect was noticed, there only remained vision in the upper nasal half of the right eye, with central acuity $\frac{6}{60}$.

The patient was not seen again for four years. He was then completely blind, and was suffering from giddiness, headaches and attacks of vomiting. He was drowsy, with subnormal temperature, slow pulse, adiposity and increased sugar tolerance. The X-ray examination now showed the clinoid processes to be deficient.

Death took place shortly after a bilateral subtemporal decompression operation undertaken for the relief of the general pressure symptoms.

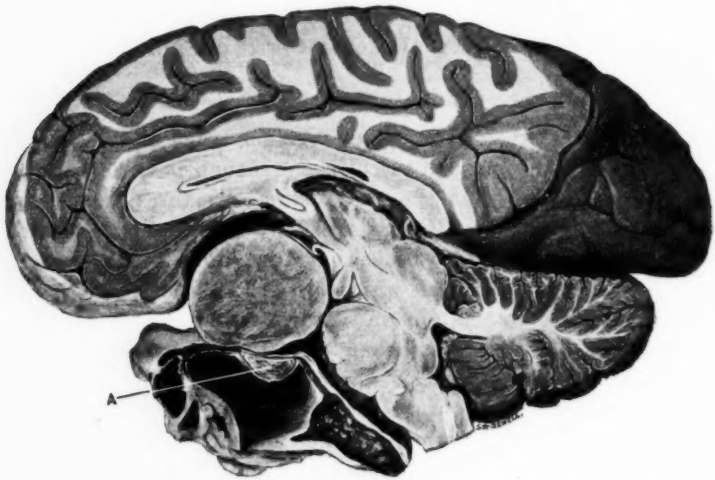

FIG. 1.—A drawing of a mesial sagittal section of the brain in Case 1, showing the position and relations of the tumour. (Reproduced from *British Journal of Surgery*, 1924, **11**, 524.) A, pituitary body.

The tumour and its relations are well shown in the accompanying illustration (fig. 1). It is a firm, spherical, encapsulated mass of growth resting upon the diaphragma sellæ, and attached only to the dura near the anterior clinoid processes.

Case 2.—J. V., male, aged 55, was admitted to the National Hospital in May, 1914, complaining of progressive failure of vision for two years. He first noticed a mist creeping over the left eye from the outer side, which gradually extended over the whole field. Six months after the onset the right eye began to be affected similarly; here again the mist encroached from the outer

side. He complained of no other symptoms, and had had no headache or vomiting.

On admission the left eye was found to be completely blind, whilst he had only perception of hand movements in the nasal field of the right eye. The discs were pale, the pallor being more marked in the left than the right, and in the temporal than the nasal half of the right disc. Smell was normal, and there was no adiposity and no somnolence or disturbances in hair distribution.

Operation.—The chiasma was exposed by the left frontal route, and a large quantity of soft reddish tumour was removed piecemeal. Post-operative recovery was uneventful.

He was seen four months later with vision considerably improved.

Case 3.—A. P., a married woman, aged 49, was admitted with a history of headaches and deterioration of vision for twelve months. The left eye was

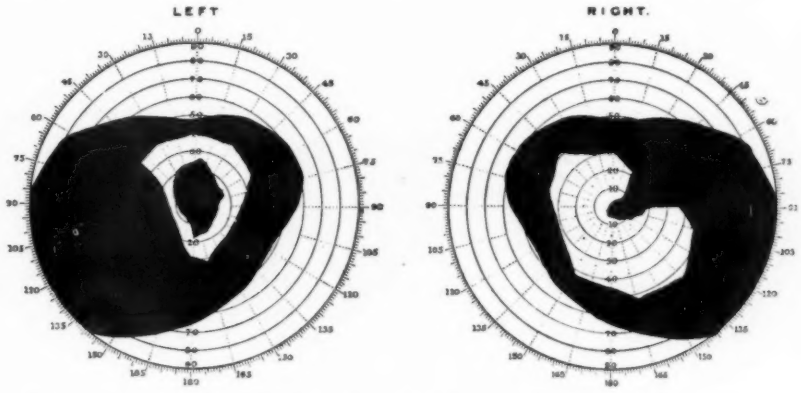

FIG. 2 (*Case* 3).—Visual fields to white charted on a McHardie perimeter with a circular object 10 mm. in diameter.

first affected. Her memory had become dull, and the sense of smell poor. She was drowsy, and suffered from polyuria. The menstrual periods, however, continued to be regular. She had had no headache or vomiting. Her systolic blood-pressure was 148. Three months before she came under observation her visual fields were charted at Moorfields Ophthalmic Hospital (fig. 2).

On admission the discs were pale, especially in the temporal halves. There was perception of light in the right eye and in the nasal field of the left eye. X-ray examination showed no abnormality of the sella.

Operation.—February 16, 1923. A right frontal osteoplastic flap was turned down and the dura opened. The very high intracranial pressure was reduced by lumbar and callosal punctures. On elevating the frontal lobe a dark granular tumour was seen lying over the sella, and a great deal of this was removed. It proved to be an endothelioma.

Post-operative recovery was good, but a month later there was no return of vision and the mental state had not improved.

Case 4.—E. C., a married woman, aged 45, was admitted under the care of Dr. James Collier, complaining of headaches and deterioration of vision for fourteen years. The blindness began on the left side of the left eye and progressed towards the centre and then upwards. Five years ago loss of vision began in the right eye and pursued the same course as on the left side. Some five months ago she had a fit, and since then she has had several similar attacks.

On admission the left eye was blind, and only a small centre area of vision remained in the nasal field of the right eye (fig. 3). Both discs were atrophic. There was a slight right hemiparesis. She was six months pregnant. There was no obesity or loss of hair. X-ray examination showed a normal sella turcica.

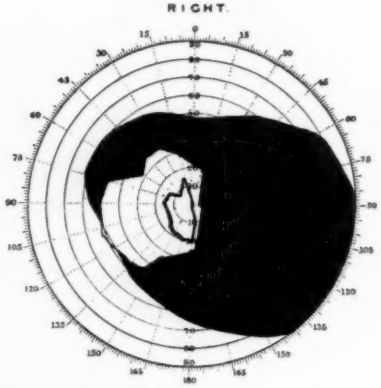

FIG. 3 (*Case* 4).—The visual fields of the right eye with a white object 5 mm. in diameter. The inner line represents the field before operation, the blackened part that blind after operation.

Operation.—January 23, 1925. Left frontal osteoplastic approach. The intracranial pressure was high, necessitating lumbar puncture. A large quantity of tissue was removed from within the capsule of the tumour, which lay above the diaphragma sellæ. The chiasma was not seen.

The patient made a good recovery, and subsequently gave birth to a child normally. Readmitted twenty months later, there was perception of light in the nasal field of the left eye which had previously been quite blind; she could count fingers in the nasal field of the right eye, the temporal half being lost. She was suffering from olfactory hallucinations and uncinate epilepsy, and was treated by X-rays.

Six months later she was still suffering from uncinate attacks, and there was some weakness of the right limbs.

Case 5.—J. H., a male, aged 30, was admitted to the National Hospital in June, 1926. During the war he was wounded in the chest; his health had otherwise been good.

His right eye had been amblyopic since childhood. Three years before he came under observation the sight of his left eye began to fail from the temporal side, and the vision deteriorated gradually. Three months ago headaches became troublesome and he had a few attacks of giddiness, but no vomiting. His general health remained fair, and there had been no change in weight or loss of sexual power.

There was no abnormal fat or change in hair distribution, and no abnormal somnolence. His visceral organs were normal and the systolic blood-pressure was 135. Smell was unaffected, the ocular movements were normal and the pupils reacted to light and on accommodation. No disturbance of function was present in the other cranial nerves, in sensation or in the reflexes.

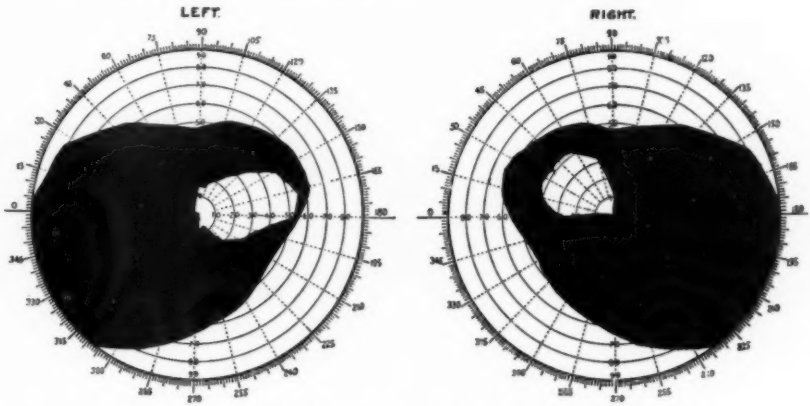

FIG. 4 (*Case* 5).—Visual fields to white charted with an object 1° in diameter.

The vision of his right eye was so reduced that he could not count fingers; with the left he read $\frac{6}{36}$. Only a small area of vision remained in the upper nasal quadrant of the right eye; in the left there was complete temporal hemianopia and a generally restricted nasal field (fig. 4). Both optic discs were in a state of primary optic atrophy. X-ray examination revealed a normal sella turcica, with no shadow in its neighbourhood. The blood-sugar curve was within normal limits.

Operation.—June 11, 1926. A right frontal osteoplastic flap was made; the intracranial tension was only slightly raised. On opening the dura and elevating the frontal lobe a tumour was found between the optic nerves and above the diaphragma sellæ; part of it was removed. After a period of restlessness the patient died thirteen days after the operation without apparent cause.

The tumour is very similar to that in Case 1, in its position, relations, and attachment to the dura of the sellar diaphragm. Posteriorly, however, it is more lobulated, and the lobules are so disposed as to wrap round one of the anterior cerebral arteries (fig. 5).

Case 6.—A. B., an unmarried woman, aged 47, came under observation in October, 1924. Her past health had been good, apart from dyspepsia; in 1915 a gastro-enterostomy was performed, probably for a duodenal ulcer.

In 1912 she discovered on covering her left eye that the vision of her right eye was affected; this became gradually worse till she could see with "the inner corner of the eye only." Since 1917 this eye had been blind. In 1918 the vision of her left eye became similarly affected and had deteriorated gradually; for some time she had been able to see "from its inner corner only."

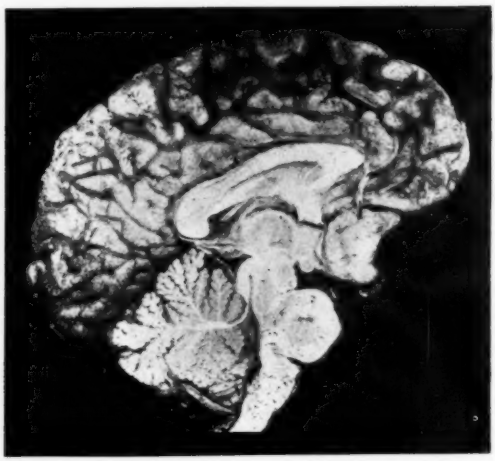

FIG. 5 (*Case* 5).—Photograph of a mesial sagittal section of the brain showing the tumour. The pituitary body is seen intact but somewhat flattened on its inferior angle, separated from the tumour by the diaphragma sellæ.

In 1915 the right disc was atrophic, and in 1922 the left disc was also pathologically pale.

In 1919-20 she suffered considerably with headache and vomited occasionally, but this may have been due to indigestion. In March, 1924, she had an epileptiform convulsion, and two more during the summer of that year; there was no warning, and in one attack which was observed the left side of her body was more convulsed than the right.

She was a thin, pale woman, but there was no abnormality in her figure or in hair distribution. Menstruation had been regular until a few months before we saw her. Her pulse was slow, and her systolic blood-pressure 135. There was a slight degree of weakness of the left side of the face and of the left arm,

but no disturbance of sensation; the left tendon-jerks were exaggerated, the left abdominal reflex absent, and the left plantar extensor in type. The ocular movements were normal, and she had never had diplopia. The right pupil reacted only consensually to light, the left directly. Smell was unaffected.

She had no perception of light in the right eye; in the left central vision was less than $\frac{6}{60}$. In the left eye there was a complete temporal hemianopia and the blindness extended about 4° over the fixation point into the nasal field (fig. 6). The field for red was of fair size in the nasal half of the field. X-ray examination showed a flattening of the sella turcica, absence of the right anterior clinoid processes, and erosion of the bone at its base.

Operation.—November 7, 1924. A right frontal osteoplastic flap was turned down, the dura opened, and the frontal lobe elevated. The general

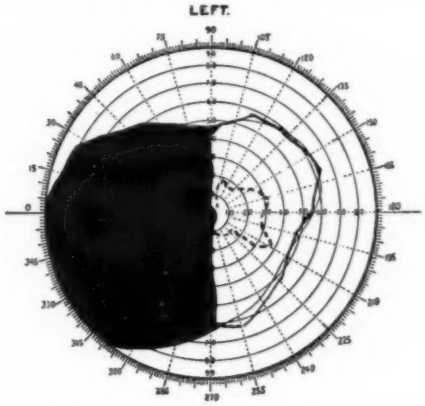

FIG 6 (*Case* 6).—Field of the left eye charted with a white object 5 mm. in diameter. The broken line represents the field for a red object of the same size.

intracranial pressure was only slightly greater than normal. A soft lobulated tumour was seen lying just above the sella turcica, and this was partly removed. Its relation to the chiasma could not be definitely ascertained. Histologically the tumour proved to be a psammoma. Post-operative recovery was uneventful. When she left hospital on November 28, there was a very slight weakness of the left arm and face; the left plantar reflex was extensor, and the left abdominal reflexes absent. Sense of smell was lost on the right side. Central vision in the left eye had improved to $\frac{6}{18}$.

Case 7.—A. B., a female, aged 50, had never enjoyed robust health. In 1925 her right antrum was drained for septic trouble.

She came under observation in September, 1926. Two and a half years previously the vision of her right eye had become dim, especially in the temporal side of the field, and it deteriorated gradually, until in March, 1926, the right eye was blind. In September, 1925, the vision of her left eye began

to fail, but she could not say in what portion of the field the defect first appeared. During the spring of 1926 she was given a series of X-ray applications to her head on the assumption that a pituitary tumour was present, and after these the vision of her left eye improved slightly. For almost two years she had suffered with slight frontal and vertical headaches, and occasional attacks of dizziness, but she had not vomited. There was no history of diplopia. She had lost about 14 lb. in weight during her illness and she tired easily. Menstruation still continued, but had lately become irregular; there were other signs of the natural menopause.

She was a healthy looking and well-nourished woman; there was no excess of fat or abnormality in the amount or distribution of her hair. Her breasts were well developed and firm. All her visceral organs were normal; her systolic blood-pressure was 150 and the diastolic 90. Her right eye was com-

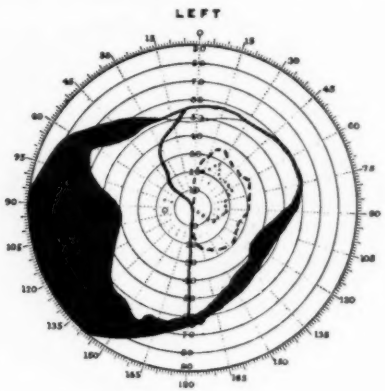

FIG. 7 (*Case* 7).—The blackened area represents the blind area on September 25, 1926, the continuous line the inward limit of the temporal defect on October 26, 1926. The broken line encloses the field for red on September 25, 1926, the doted line the red field on October 26, 1926. All fields were charted with 10 mm. objects.

pletely blind, and the central vision of her left was $\frac{6}{9}$ when fully corrected. The nasal side of her left visual field was normal, but the temporal side was contracted to almost 30°, and there was a small temporal paracentral scotoma extending almost up to 3° from the fixation point (fig. 7). Red vision was lost to the temporal side of the fixation point. In both optic discs there was a moderate amount of atrophy of the primary type. Her left pupil contracted well to light, the right only consensually. There were no other signs of nervous disease. X-ray examination showed a slightly flattened but elongated sella turcica; the posterior clinoid processes were massive and well developed, the anterior processes were possibly a little depressed, but probably not pathologically.

During the succeeding month the headaches became more severe, and her

vision deteriorated till she had a temporal hemianopia in the left eye, complete except in the upper quadrant.

Operation.—November 3, 1926. Left frontal osteoplastic flap. The intracranial pressure was not raised. A large solid tumour was seen, presenting medial to the optic nerve, which was pale and small. A large quantity of the tumour was removed, the structure of which proved to be that of an endothelioma. Post-operative recovery was completely uneventful.

Three months later she was reported as being in excellent health. The left visual field had enlarged slightly, with acuity $\frac{6}{18}$. In July, 1927, her health was still good, she was still free from headaches, but the vision of her left eye had lately deteriorated to $\frac{6}{60}$, and there was again an almost complete temporal hemianopia.

Case 8.—P. B., a male, aged 48, came under observation in April, 1925.

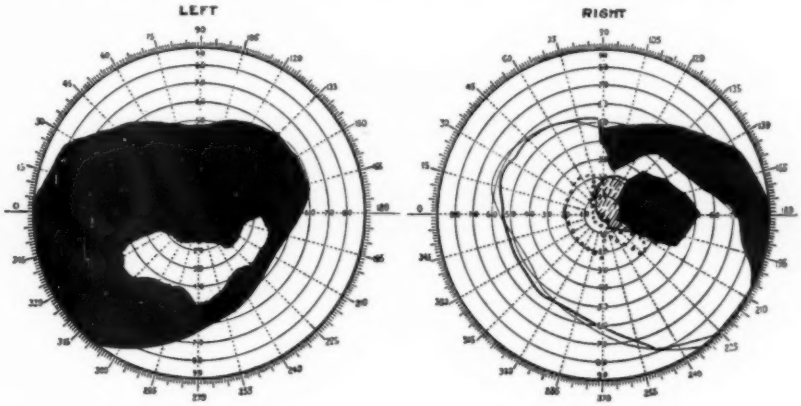

FIG. 8 (*Case* 8).—The blackened areas represent blindness to a white object 5 mm. in diameter, the shaded portion an area of amblyopia. The dotted line encloses the field for red in the right eye.

His previous health had been good; the Wassermann reaction in his blood was completely negative.

A year ago he found he could not see print distinctly with his left eye; from this time its vision deteriorated rapidly. Eight months ago the sight of his right eye began to fail and had since become progressively worse. There had been no diplopia, no headaches and no vomiting. He had increased considerably in weight, due probably to inactivity, and had become drowsy and apathetic. No loss of hair had been noticed and sexual power remained unimpaired.

He was a pale, coarse-looking man. Hair distribution was normal and the testes were well developed. The visceral organs were normal and the blood-pressure was 135. There was no evidence of intracranial disease, apart from the disturbance of vision.

He could read only $\frac{6}{24}$ with the right eye; in the left he could perceive hand movements in the lower portion of the fields only. The field of the right eye was contracted in the upper temporal quadrant, and there was a large temporal paracentral scotoma lying mainly above the horizontal, with a slight defect to white at the fixation point. To a red object, 10 mm. in diameter, there was a complete central scotoma, but the colour could be seen in the rest of the nasal field and in a small area in the lower temporal quadrant (fig. 8). The left optic disc was very pale and had sharply-cut edges, but the vessels were normal; there was a general pallor of slight degree of the whole right disc.

Operation.—On April 19, 1925, an operation was performed by a left frontal osteoplastic flap. The dura was opened (after lumbar puncture to relieve the intracranial pressure), and the brain elevated. A firm, solid,

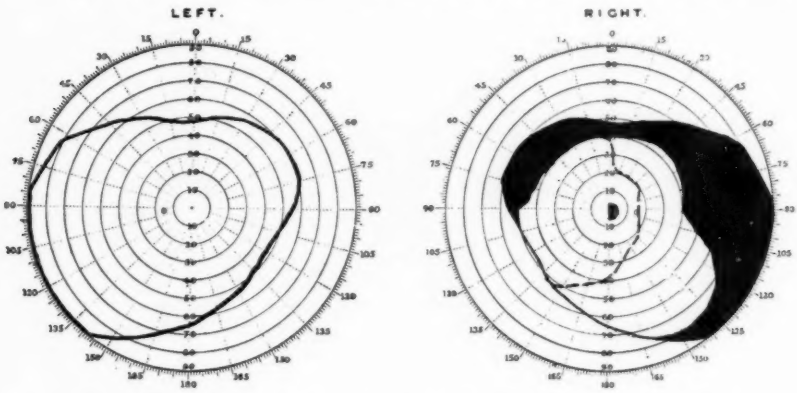

FIG. 9 (*Case* 9).—The blackened areas represent the loss of vision in the right eye to a $\frac{20}{330}$ white object in May, 1921; the broken line the margin of the temporal defect to a $\frac{6}{330}$ object. (Fields taken by Dr. H. M. Traquair.)

granular tumour was at once encountered, projecting on to the orbital roof. Its capsule was incised and a large mass of tumour was removed. The outer part of the capsule was then cut away. It proved to be an endothelioma of, apparently, a rather rapidly growing kind (Greenfield).

Post-operative recovery was uneventful. The patient became brighter and left the Home greatly improved. His vision, however, failed to improve, and in December, 1925, he was reported as being "quite blind, but wonderfully well and cheery."

Case 9.—M. J., an unmarried woman, aged 44, came under observation in March, 1923. Her previous health had been excellent and menstruation continued regularly.

In December, 1920, she found the vision of her right eye defective, and had some orbital pain at this time. In May, 1921, Dr. H. M. Traquair, under

whose care she was, found the vision of this eye less than $\frac{6}{60}$, the disc pale, with relative failure in the temporal field and a central temporal hemianopic scotoma; the left eye was normal (fig. 9). In February, 1922, she could count fingers only with the right eye, and the vision of the left was reduced to $\frac{6}{12}$ with temporal restriction of its field. In January, 1923, she could count fingers in the nasal portion of the right field, and with the left eye she read $\frac{6}{60}$. In the field of the left eye there was relative temporal loss and a central hemianopic scotoma in the temporal side (fig. 10). The left disc was normal. Since December, 1920, she suffered with headaches, at first in the right temporal region, lately on the left side too. She had not vomited. For the past three months she had had double vision. For ten years, at least, she had been subject to "day dreams," in which she felt that there was "something menacing in front of her, nothing physical or concrete, as if a spirit were pulling

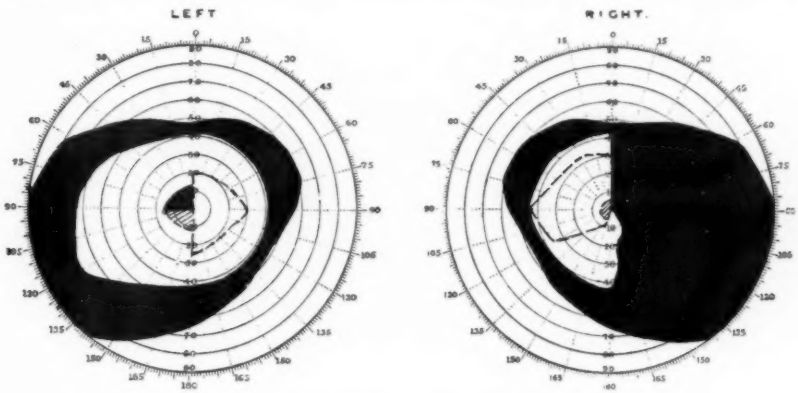

FIG. 10 (*Case* 9).—The blackened areas show the loss of vision in January, 1923, to a $\frac{50}{330}$ white object, the broken lines the fields to a $\frac{5}{330}$ object. The shaded areas indicate partial scotomata. (Fields taken by Dr. H. M. Traquair.)

her away, or as if something were trying to catch her." In these states she was fully conscious of her surroundings, and yet the day dreams were very real and vivid.

She was a healthy well-nourished woman, without any peculiarity in the distribution of hair or fat. The breasts and areolæ were well developed. Sugar tolerance was normal.

In March, 1923, she had only a little vision in the nasal portions of both fields, more in the left than in the right. Both discs were atrophied, especially the right, but there was no other fundus change and the retinal vessels were normal. Smell was poor, particularly on the left side, but not lost in either nostril. Both pupils reacted to light more briskly when it fell on the temporal sides of the retinæ. There was no ocular palsy, and no disturbances in the motor functions, in sensation or in the reflexes.

Operation.—April 14, 1923. A right-sided frontal osteoplastic flap was turned down. The general intracranial pressure was rather high, rendering approach to the chiasma somewhat difficult. The escape, however, of an unusually large quantity of cerebro-spinal fluid from the base allowed the frontal lobe to be safely elevated, when an encapsuled lobulated tumour was exposed, projecting from below the chiasma and between the two optic nerves. The right nerve was evidently under great tension. A large quantity of tumour tissue was removed from within the capsule, which procedure obviously relieved all tension on the nerves and chiasma.

Post-operative recovery was very good, except for a rather unusual amount of headache. The tumour was an endothelioma.

Subsequent history.—Eighteen months after the operation Dr. Traquair reported that the right eye had now no perception of light, and the left only a small dim patch in the nasal field. "Headaches are not at all bad, and there is no sign of the tumour enlarging upwards."

Case 10.—Mrs. H., a woman aged 47, was first seen in December, 1926. Her past health had been excellent; she had two children and menstruation ceased in a natural climacteric a few months before we saw her.

Two years previously she had noticed a "darkness" coming over her left eye from the temporal side; this increased gradually, and for about a year she had been completely blind in this eye. In June, 1926, she regained for a week or two some vision in her left eye. In May, 1926, she found the sight of her right eye defective; she failed to see objects, such as a tennis ball, near the line of direct vision, and from this time her sight deteriorated gradually from the centre outwards towards the right side. She had never had double vision. Two months before she came under observation she had a series of headaches, chiefly bitemporal and occipital, and her left eye had become painful; no vomiting had occurred.

Her general health remained good; she had increased about 7 lb. in weight in the past six months, due she believed to her less active life. She was bright and intelligent, though naturally depressed at the prospect of losing her sight. Her visceral organs were normal; the systolic blood-pressure was 135 and the diastolic 80. She was well nourished, and there was no abnormality in the distribution of fat or hair.

Her left eye was totally blind, while the central vision of the right was reduced to less than $\frac{6}{60}$. In this eye there was an almost complete temporal hemianopia, and in addition some defect of central vision for white, and complete central loss to red and green. The periphery of the nasal field was normal (fig. 11A). Both optic discs were pale, especially the left, but no other changes were visible in the fundi; the retinal vessels were of normal size and appearance. The left pupil reacted only consensually; the right contracted directly to light and on accommodation. The functions of the other cranial nerves, including smell, the motor system, sensation and the reflexes, were all normal. X-ray examination revealed no enlargement or distortion of the sella, and no shadows above it.

Operation.—January 5, 1927. The skull was opened by a right osteoplastic flap. The intracranial pressure was low. On raising the frontal lobe a firm, spherical tumour was seen to the medial side of the right optic nerve. The nerve was surrounded by a lobule of this tumour, which was cut away. On working backwards, a round mass was found lying between the optic nerves and below the chiasma; it was gradually loosened from its surroundings and removed whole. The left optic nerve then came into view; it was flattened by pressure and very white.

The tumour was almost spherical and measured $2\frac{1}{2}$ cm. in diameter. Its structure was that of an endothelioma.

The patient recovered rapidly from the operation. Twelve days later she was able to read $\frac{6}{12}$ and + J4 with the right eye, and the only defect in the field of vision was loss of perception of green on the temporal side of the fixation point; here red appeared as orange (fig. 11, B). The left eye remained blind.

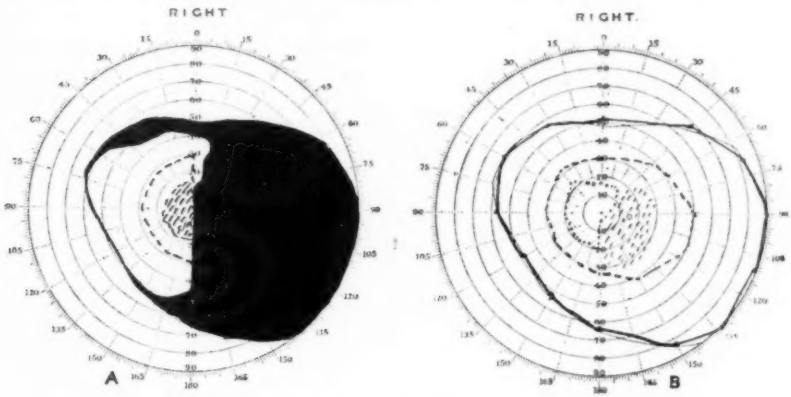

FIG. 11.—**A** shows the field of vision in the left eye on December 31, 1916, taken with objects 5 mm. in diameter. The blackened area indicates complete loss of vision, the shaded area a partial scotoma for white, and the broken line the outline of the field for red. There was no green vision.

B represents the field of vision of the same eye to 5 mm. objects on January 17, 1927, twelve days after operation. The broken line includes the field for red, the dotted line the field for green. In the shaded area red vision was defective and vision for green was lost.

On July 1, 1927, her left eye was still blind. She said her right eye was "as good as ever it had been," and with it she read $\frac{6}{6}$ and J1. No disturbance could be detected in any portion of the field. She had been free from headache and other symptoms.

DIAGNOSIS.

When we come to consider the differential diagnosis of endotheliomata in the neighbourhood of the chiasma we find they present no pathognomonic signs, though certain clinical features tend to separate them from

the more common pituitary growths, and from tumours of the infundibular region; we may hope that a more intensive study and further experience will enable us to recognize this type of tumour with more certainty.

Six of our patients were women, and four men; most of them were between 45 and 50 years of age, the youngest being 30 years and the oldest 55 years.

The duration of the symptoms varied between one and fourteen years before they came under observation; in the majority it was between two and five years, but in two the symptoms had only lasted eighteen months. Headache was a prominent symptom in that case only in which the tumour grew very rapidly; and it usually set in long after the disturbance of vision was noticed. Two at least of the patients never suffered from headache, and in some of the others it was slight. When present it was usually frontal, but one woman complained mainly of bi-temporal pain. Two patients were subject to vomiting, but in one this was probably independent of the tumour, as she had had no headache or other symptoms of increased intracranial pressure. In two cases there were clinical evidences of pressure upon or involvement of the brain, in the form of a slight hemiparesis; in one of these the symptoms had lasted twelve years, in the other fourteen years. These two patients were subject to epileptiform seizures in which the palsied side was probably more severely involved. Another patient had typical dreamy states, indicating that the tumour compressed the medial side of the temporal lobe. A disturbance of smell was noted in two cases, and in one diplopia had occurred.

There was nothing characteristic in the visual symptoms, or at least no special features which would enable one to distinguish by this means alone between these and other growths compressing the optic nerves or the chiasma. In all, except in one of the acute cases, the sight of one eye was affected a considerable time before that of the other, in one case by as much as five years. This indicates that, as the pathological examinations and the operative observations show, the optic nerves are first compressed and the chiasma suffers only when the tumour has become larger.

Two patients gave a history of a sudden disturbance of vision in the eye first affected, but it is well known that a considerable amount of amblyopia may be present in one eye until discovered by accident. In two cases a temporary improvement of vision occurred, apparently independently of treatment; one woman stated that for some weeks she was able to see again with an eye which had been blind.

The changes in the visual fields resemble those produced by pituitary tumours and other growths which compress the chiasma or optic nerves, the only noteworthy difference being that in endotheliomata there is often a striking asymmetry, the one eye being affected long before the other, or the loss in the one field being much greater; but this is often seen in pituitary and stalk tumours too. The most characteristic features are a loss of vision extending in from the temporal periphery and progressing to a hemianopia and later to blindness, first in the one eye and then in the other; or a central or temporal paracentral scotoma, usually associated with constriction of the temporal periphery when the patient came under observation. The histories of two cases at least suggest an onset with a central loss of vision in one eye. In all there was a greater defect of colour vision than of vision to white.

In all our cases the ophthalmoscope revealed a state of primary optic atrophy; there was never any trace of œdema or swelling of the disc, and never any changes suggesting that a papillœdema had preceded the atrophy.

Differential Diagnosis.

The two most important conditions which must be considered in the differential diagnosis of endotheliomata are tumours of the pituitary body and growths arising in connection with the infundibulum, especially from Rathke's pouch.

From pituitary tumours the endotheliomata can be usually distinguished by radiographic examination, for the latter never produce the distension and "ballooning out" of the sella turcica which is characteristic of intrasellar growths. The sella is usually normal, or it is merely flattened by pressure from above, but the clinoid processes may be eroded, especially when the tumour is large. Further, in our series of cases there were none of those symptoms which have been attributed to disturbance of pituitary function, and especially to hypopituitarism, such as adiposity, anomalies in hair distribution, changes in carbohydrate metabolism and disturbances in the functions of the sexual organs. Even in the two largest pathological specimens which we have seen the pituitary was only moderately compressed and probably remained functionally active. Four of our patients were drowsy and two slept excessively, but these symptoms were probably in part due to the inactivity associated with blindness. In one case only was there that pathological somnolence so often seen in patients with pituitary adenomata.

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The distinction of endotheliomata from tumours growing from the infundibular stalk is less easy, as the latter do not produce the characteristic radiographic appearances which are found with pituitary growths. The sella is, however, often large, though rarely distended to the same extent. More frequently the clinoid processes, and especially the posterior, are indistinct or eroded, a condition often found with endotheliomata. Suprasellar shadows, which constitute the most characteristic radiographic feature in cases of stalk tumour, are by no means constant; they were visible in only five out of the ten cases we have collected for comparison.

Case	Sex	Age	Duration	Headache	Vomiting	Smell	Diplopia	Obesity	Hair	Menstruation	Sexual power	Somnolence	Blood-pressure	Optic discs	X-ray of sella
ENDOTHELIOMATA.															
1	M.	41	5 yrs.	Late	0	+	0	+	+			+		Atrophy	Normal
2	M.	55	2 yrs.	0	0	+	0	0	+			0		Atrophy	
3	F.	49	1 yr.	++	0	−	0	0	+	+		0	148	Atrophy	Normal
4	F.	45	14 yrs.	+	0		0	0	+	+		0		Atrophy	Normal
5	M.	30	3 yrs.	Late	0	+	0	0	+		+	0	135	Atrophy	Normal
6	F.	49	12 yrs.	+	0	+	0	0	+	+		0	135	Atrophy	Normal
7	F.	50	2½ yrs.	+	0		0	0	+	+		0	150	Atrophy	Normal
8	M.	48	1 yr.	0	0	+	0	+	+		+	+	135	Atrophy	Normal
9	F.	44	3½ yrs.		0	−	+	0	+	+			130	Atrophy	Normal
10	F.	47	2 yrs.	+	0		0	0	+	+		0	135	Atrophy	Normal
STALK TUMOURS.															
1	F.	34	2 yrs.	++	+	+	0	++	0	0		++	128	Œdema	Normal
2	M.	11	3 yrs.	++	+	+	+	+	0			+		Œdema	Normal
3	M.	10	½ yr.	++	+	+	+	++	0		0	+	106	Œdema	Enlarged
4	M.	39	2 yrs.	+	0	+	0	+	+		0	+	112	Atrophy	
5	M.	54	3 yrs.	++	0	+		+	0		0	+	140	Atrophy	Normal
6	F.	27	10 yrs.	++	+	+	+	++	0	0		+	110	Atrophy	Enlarged
7	M.	60	1 yr.	+	0		0	+	0		0	++	108	Normal	Enlarged
8	F.	18	2 yrs.	++	+		0	+	0	0		+	100	Atrophy	Enlarged
9	M.	12	4 yrs.	0	0		0	++	0			++		Atrophy	Enlarged
10	M.	36	2 yrs.	+	+		+	+	0				124	Atrophy	Normal

It is therefore mainly on the clinical features that we must rely for the differential diagnosis. The age incidence may be some help, for while endotheliomata occur chiefly after 40 years of age, in seven in a series of ten consecutive stalk tumours we have observed the patients were under 36 years of age when they came under observation. In a considerable portion of stalk tumours the symptoms appear within the

first two decades. Again, headaches, which are rarely a prominent and usually a late symptom in endotheliomata, are almost invariable in stalk tumours, and are often early and very severe.

There was a history of cerebral vomiting in only one of our patients, but it occurred in six out of the ten cases of stalk tumour which we have collected for comparison.

The constitutional symptoms differ more markedly in the two groups. Adiposity of the dyspituitary type is very common in the stalk tumours, while it was present in pathological degree in one only of our cases of endothelioma, and here it was partly at least due to inactivity. Again, in our series of cases we met no instance of loss or abnormal distribution of hair; but the hair, apart from that of the scalp, was scanty, infantile, or in men of feminine distribution, in all but one of the cases of stalk tumour. Most of these cases were also pathologically drowsy or somnolent. Carbohydrate metabolism, as measured by the blood-sugar curve after the administration of glucose, was normal in all cases of endothelioma in which it was tested.

The functional state of the sex organs was an even more striking point of difference between the two groups. In stalk tumours, cessation of menstruation in women and loss of sexual power in men is almost the rule, but menstruation remained regular in all the six women with endotheliomata whom we have seen, except in one who was then pregnant, and sexual power was unimpaired in two of the men; unfortunately no record of this was made in the notes of the other two men.

In the six cases of endothelioma in which it is recorded in our notes, the blood-pressure was normal in relation to the age of the patient, while it was abnormally low in the patients with stalk tumours, except in two in whom there was severe headache and other evidences of considerable rise of intracranial pressure at the time it was taken.

Finally, when the optic nerves are compressed by an endothelioma, the ophthalmoscopic picture seems to be invariably one of simple primary optic atrophy, while papillœdema or a consecutive atrophy of the discs is present in a considerable proportion of stalk tumours; in a series of adamantinomata collected by Critchley and Ironside, papillœdema was found in eight and primary atrophy in five.

By these symptoms it is generally possible, we believe, to distinguish clinically between suprasellar endotheliomata and tumours arising in connection with the cranio-pharyngeal pouch.

The distinction between these two forms of suprapituitary tumour

is of great practical importance when an operation is contemplated. First, a stalk tumour cannot be extirpated, as it lies further back and higher up than an endothelioma, whilst its close relationship with the third ventricle and hypothalamus would alone rule out any attempt at total removal. An endothelioma, on the other hand, can, if small, be completely and safely removed, and it seems probable from a study of the origin, rate of growth, and relations of these tumours, that in most or perhaps in all of them there must have been a time when total removal would have been possible. Again, partial removal of a stalk tumour, whether cystic or solid, may be followed by severe and even fatal toxic symptoms; no such complication arises from the operative disturbance of an endothelioma. Further, patients with hypopituitary symptoms, especially with a low blood-pressure, such as many of the stalk tumour cases manifest, are greater "surgical risks" than those with normal blood-pressure and normal pituitary function. Consequently, in cases of stalk tumour the operative mortality is higher, whilst the prospect of substantial and lasting benefit is smaller.

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DISCUSSION.

Dr. E. Sachs thought that in one of the points Mr. Sargent made in the paper he had been somewhat too radical, namely, in what he said about stalk tumours. The speaker agreed that these were much more difficult to deal with surgically, but in the cases in which they were practically entirely cystic it had been possible, in a few cases, to empty the cyst and remove the cyst wall. A serious feature was the fact that they compressed the hypothalamus, and that was why so many proved fatal after operation. But it was possible—and in the future it would probably be possible more frequently—to remove these stalk cysts. Of course, when the stalk tumour was solid, the problem was a graver one, and at present he did not know of an instance in which a solid stalk tumour had been removed.

Dr. Wilder Penfield said it was of the utmost importance to collect such a group of cases of endotheliomata at the base of the skull, as they were very rare, and it was only from a large experience, such as that of Mr. Sargent and Dr. Holmes, that such a collection could be made. In reviewing, in Dr. Greenfield's laboratory, a long series of intracranial tumours, which were made

available to him through the kindness of the Staff at the Queen Square Hospital, he was able to find records of ten cases of endothelioma which had invaded the overlying skull; there was no case in which there was invasion of the bone at the base. He asked Mr. Sargent to say whether any of those in his report had invaded the bone at the base of the skull. If none had, that negation would lend support to the theory, first put forward by Spiller, that in the endotheliomata which invaded the overlying skull, there had always been previous local trauma of the vault of the skull. Of local trauma to the base it would be very difficult to conceive.

Mr. SARGENT, in reply, said that involvement of bone was one of the points he did not refer to. In none of the cases included in this paper had the bone been invaded.

In reply to Dr. Sachs as to the cystic tumours, it was possible to remove part of the cyst wall, as well as to empty the cyst. He had removed, at a second operation on one of these cases, not only part of the cyst wall, but what was practically a tooth which was projecting into it, for adamantinomata resemble closely tumours found in the gums.

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RECOVERY AFTER SEVERANCE OF CUTANEOUS NERVES.

BY SIR E. SHARPEY SCHAFER, F.R.S.
(*Edinburgh.*)

I HAVE lately been making some experiments upon myself, the primary object of which was to determine the relative rate of recovery of sensibility after severance of cutaneous nerves: (*a*) By simple transection; (*b*) by squeezing with artery forceps. In both cases there will be complete peripheral Wallerian degeneration as the result of severance of the continuity of the axis-cylinders—but in (*a*) the re-growing nerve-fibres must find their way to the part of the skin which they supply through the cicatricial tissue and neuroma formed between the severed ends, whilst in (*b*) the axis-cylinders would have the original sheaths, both connective and neurolemmal (sheath of Schwann), along which they could directly grow as single fibres without—as Langley showed—the budding out of a number of branches from the cut ends in the proximal stump. It was to be expected that recovery would progress more rapidly in (*b*), and also that it might be more complete. These expectations have, as will be seen, been realized.

The first operations were performed for me by Mr. Norman Dott on October 11 of last year under local anæsthesia (novocaine with adrenaline). The nerve selected was the posterior (ulnar) branch of the internal cutaneous nerve of the forearm. The nerve of the left arm was *cut through*; that of the right arm was *tightly pinched* for two or three seconds with Spencer-Wells forceps and then released; the wound was closed by two or three sutures and healed rapidly by first intention.

The effect of the local anæsthesia passed off within a few hours. The next day, on testing the area supplied by the nerve for various forms of sensibility, I was surprised to find that in neither case had anæsthesia been produced. All forms of cutaneous sensibility were still present, but over the whole area there was a peculiar sensation on being touched or stroked which can only be described as a feeling of "numbness"; this was sufficiently definite to enable one to mark out with fair exactitude the implicated area. Testing by v. Frey bristles and by stroking with cotton wool and a fine camel-hair pencil showed slight diminution of tactile sensibility, although no distinct difference to warmth and cold, nor to the prick of a needle, could be determined. All forms of sensibility showed the punctate character which is peculiar to cutaneous sensations.

Consideration of the conditions of the experiment soon made it clear that a result such as that obtained might have been expected. For in most cutaneous areas there is a greater or less overlap of the cutaneous nerves, and in the case of the particular nerve selected it is known that it receives, below the point of severance, a considerable branch from the posterior (radial) division of the internal cutaneous—so that the area supplied by it would be by no means denervated. I was not at the time aware of this incursion of intact fibres, but even had I been I should certainly have expected a greater result in the direction of anæsthesia than showed itself in these experiments. Within a few hours of the operation—probably from the time of the passing off of the effect of the local anæsthetic—a burning, tingling pain was felt; this was referred to the area supplied by the nerve, and was produced no doubt by changes occurring at the point of severance. Before very long this somewhat acute pain subsided; but within a few days a less acute but very unpleasant sensation of the same kind, and also referred to the area to which the nerve was distributed, gradually developed; this painful sensation lasted for some weeks on the left (cut) side, but a less time on the right (squeezed) side, where it was never so severe. Being a continuous and not an intermittent sensation, it was often not noticed unless the attention were directed especially to it. It was probably due to the formation and contraction of cicatricial tissue which stimulated the growing ends of the "pain" fibres; the sensations caused thereby would naturally obscure any which might be caused by stimulation of the severed "special sense" fibres; just as, when we stimulate the ulnar nerve at the elbow (funny-bone) by mechanical means, such as a blow, we produce merely a confused sensation of pain without our being able to distinguish the special varieties of sensation. After lasting a few weeks the continuous painful sensation gradually and completely disappeared.

The main object of the experiment was decisively attained. On the left (cut) side the condition of the implicated area has remained such as has been described, i.e., there is a feeling of "numbness" on stroking it, and a slight diminution in tactile sensibility. But there was presently added to it the hypersensitiveness to pain which has been described by all who have investigated the subject [Head and Rivers, Davies and Trotter, Boring]. Head and Rivers described this as a novel and peculiar form of sensibility which they qualified by the adjective "protopathic" in contradistinction to "epicritic" sensibility, the term used by them for all forms of sensation in which qualities other than those of pain are distinguishable (touch, warmth, cold, pressure). The expression "protopathic" is, however, only a longer way of expressing

"pain" or "general sensation," and is in fact the painful sensation experienced when an area over which the pain-fibres are extending themselves is stimulated by anything more than a light touch, whilst "epicritic" expresses nothing but what has always been known as "special sensation." Growing pain-fibres appear to be unusually sensitive, and produce a painful response even to stimuli which do not usually occasion pain. Whether this is due to the fact that they are growing, or to the absence of the sheaths by which normally developed fibres are always eventually surrounded [Trotter] must be left an open question. The hypersensitivity might possibly be due, at least in part, to the fact that the pain-fibres, which have budded and are growing into all parts of the implicated area, would be more numerous than normal, and might therefore appear more sensitive because more fibres were stimulated than is usually the case. This suggestion was put forward by Professor Hartridge, at the May meeting of the Physiological Society to which I communicated some of my results, and seemed an explanation worthy of consideration. But the fact that the hypersensitiveness to pain shows itself for a time also on the side in which the severance is produced by squeezing, and in which the growing nerve-fibres do not multiply by budding, and are conducted along the old sheaths to their termination, shows that an increase in number cannot be the explanation of the hypersensitiveness of the area into which new pain-fibres are growing. Nor can it be due to the growing fibres of the special sense nerves conducting impressions of pain as has been suggested by Trotter, for such a hypothesis would ignore the Müllerian doctrine of "specific nervous energy" upon which all our conceptions of the functions of the nervous system are based. No doubt on the cut side the special sense nerves would also be growing into the implicated area, but so far as we know (as a matter of fact we know nothing certain about the endings of the warmth and cold nerves) the special sense nerves require, in order to evoke the special qualities of sensation which they subserve, to end in some special organ, such as a tactile corpuscle or modified epiderm cell. In any case the pain sensation due to stimulation of the growing pain-nerves would completely overmaster any sensations provoked by stimulation of those growing fibres whose function it is to subserve the special sensations.

The hypersensitiveness to pain tended to increase as time went on, up to a certain point, when it appeared to diminish, but it has never disappeared. It shows itself in the sharply painful sensation which is evoked by stimuli which would not otherwise be regarded as at all painful, such as pulling upon a hair or lightly pinching up a piece of skin between the thumb and forefinger. And it is often not very definitely localized. Especially it may be referred peripherally and may appear to

spread from the point stimulated: evidence that a small nerve-trunk and not a peripheral nerve-ending has been affected.

It is now more than nine months since the double operation was performed. But on the left (cut) side the hypersensitiveness is still present over the whole of the original implicated area and it is easy to map out the area by its presence. The feeling of numbness has decreased; nevertheless it is still possible to detect it over the whole area. It will be interesting to see how much longer these abnormal sensations will persist. The area over which they show themselves has not diminished in size, as it might be expected to do if new nerve-fibres are growing into it—as they undoubtedly are. It must be remembered that no kind of sensation was *lost* as the result of the section of this nerve; all forms could be recognized the day after the operation. One cannot therefore speak of a restoration of sensibility, since none was lost except the slight diminution in tactile sensibility which could be made out immediately after the operation and this may have been due to a disturbance of the vascular condition of the integument over the area to which the nerve was supplied (see below).

Comparing the effects of severance by squeezing with that produced by cutting, it may be stated that the immediate effect was identical on both sides. Over the whole area supplied by the nerve on the right or squeezed side all forms of sensation remained as on the left or cut side. The feeling of numbness was exhibited as on the cut side, and the after-pain, due no doubt to cicatrization at the point squeezed, was also experienced, although it was not so severe or persistent as on the cut side.

A marked difference on the two sides was, however, shown in the gradual diminution of the extent of the implicated area on the right or pinched side. This diminution in extent of the area could be ascertained by the disappearance both of the feeling of numbness and of the hypersensitiveness to pain. It began to be evident a few weeks after the operation, and, about three months after, the area over which these sensations were experienced had shrunk to a small patch on the lower (ulnar) aspect of the forearm. Presently this patch also disappeared, so that, at four months, sensation was in every way completely restored upon the squeezed side; whereas, as already stated, the conditions resulting from severance have persisted in an easily ascertainable form for more than nine months on the side of actual transection.

[1] It should be mentioned that a trauma neuroma was formed and could easily be felt at the point of severance on both sides, but was much less pronounced on the pinched side than on the cut side. On this it is still distinctly to be felt, although it has now almost disappeared on the pinched side.

This difference can only mean that the axis-cylinders growing from the neuromatous stump of the severed nerve have on the squeezed side, on which all the sheaths—probably even the neurolemmal sheaths—are still intact, been guided in their growth along the old sheaths to their actual former terminations, and have thus been enabled to effect a complete recovery of function in the part to which they had been distributed. Whereas upon the transected side the budded axis-cylinders have not even yet been able to reach an appropriate ending, and may never succeed in effecting real recovery. But the fact that the area which they subserve is, in the particular nerve chosen for experiment, also supplied by other fibres which had not been involved in the transection, will render such incompleteness of recovery of no great consequence to the patient. It might, however, be otherwise if a section were made of a nerve upon the integrity of which a particular area was wholly dependent.

In order to test this I selected for second experiment, in consultation with Mr. Dott, the nerves to the palmar and lateral aspects of the little finger of the left hand. As is well known the little finger is supplied wholly by the ulnar nerve. The part of this nerve which passes to the sides and palmar aspect of the little finger divides in the palm of the hand, some little distance from the base of the finger, into two branches, one of which goes to the inner or radial side of the finger and the other to the outer or ulnar side. We judged that if these divisions were both severed we ought to get complete anæsthesia of the distal parts of the lateral and palmar surfaces of, at any rate, the middle and terminal phalanges of the finger. We thought it expedient however to sever the two divisions successively, at an interval of some weeks, and to make the severance of the inner or radial division by *transection* and of the outer or ulnar division by *pinching* (squeezing).

Accordingly, on February 22 of this year, under local anæsthesia as before, Mr. Dott cut through the inner or radial division at the base of the little finger of my left hand. The section produced complete insensitiveness to all forms of stimulation of the lateral and palmar aspects and also of the very tip of the little finger, except that a sharp prick could still be just felt. There was no perceptible anæsthesia on the dorsal aspect, nor on any part of the proximal phalanx of the finger, nor on the outer or radial side. But there was a certain feeling of "numbness" on the internal and palmar aspects of the proximal phalanx; and, curious to relate—although the transection was made quite a considerable distance from the point of division of the branch of the ulnar to the little finger and still farther from its branch to the ulnar aspect of the ring finger—there was a quite perceptible feeling of "numbness" over the radial aspect of the ring finger, especially on the ungual phalanx: this we are

unable to account for. As a result of the section of the nerve there was for several weeks the same burning, tingling sensation, referred to the periphery (already mentioned in describing the first experiment on the fore-arm nerves), due to stimulation of the cut nerve-fibres in the neuroma: this sensation was both more distinct and more painful than that experienced as a result of section of the fore-arm nerve: perhaps from the section being made in a more exposed and more mobile situation: perhaps because the sheaths of these nerves of the finger are particularly thick, so that the nerve, when exposed for section, looks large in proportion to the extent of cutaneous surface which it subserves. The wound was sutured as before, healed readily, and shows but little sign of a scar.

About nine weeks later (on April 29) Mr. Dott exposed, under novocaine and adrenaline anæsthesia, the outer or radial division of the nerve and squeezed it with an artery forceps. Probably owing to the thickness of the sheath the local anæsthesia had not fully penetrated to all the nerve-fibres, and the squeeze produced a very unpleasant burning sensation referred to that side of the little finger. The wound was sutured as before and healed rapidly, leaving only a slight scar. After recovery from the local anæsthesia the squeezing was followed, like the cutting on the other side of the finger, by a continuous burning or tingling sensation, which showed itself at once, but after a few hours became less severe and eventually disappeared. But in three or four days a similar sensation reappeared. This was even more painful than that resulting from the transection of the nerve on the other side of the finger and much more so than that produced by the severance of the nerves in the forearm. The greater severity of this after-pain is perhaps due in part to the exposed and mobile situation of the trauma, in part perhaps to the cicatrization of a thicker sheath. Whatever its cause it was extremely unpleasant and lasted some three weeks, gradually disappearing. But, being continuous, unless attention was directed to it, it caused less actual suffering than might be thought, and in particular never kept me awake at night, although I might sometimes be awakened by it. This may, however, have been due to an accidental movement, active or passive, of the finger, causing the pain to be momentarily more severe.

The result upon cutaneous sensibility of the second operation was to render completely numb and anæsthetic the palmar and lateral aspects of the terminal and middle phalanges on the radial side. So that now, since there had been no sign of recovery on the ulnar side, the whole palmar aspect of those two phalanges, and the tip of the ungual phalanx, including most of the nail itself, were rendered anæsthetic to all forms

of stimulation. The "numb" parts appeared swollen and firm and smooth; the feeling was exactly as if a portion of dead material were overlying those parts of the finger.

This condition continued until about four weeks ago, i.e., about six weeks after the second operation. Sensibility in all forms of sensory stimulation then began to reappear; as it has seemed to me, simultaneously over the whole area of the ungual and middle phalanges supplied by the radial division. This sensibility was soon replaced by hypersensitivity to painful stimuli; even tactile stimuli, unless very light, are inclined to be painful. Warmth and cold are felt over the area, but I cannot locate definite spots; in any case it is difficult to locate warm and cold spots in this situation even in the normal finger. The nerve-fibres severed by squeezing have evidently grown again, and are recovering their normal functions, but the pain-fibres are hypersensitive.

On the cut side there is as yet no recovery of cutaneous sensation. But that the nerve-fibres are beginning to grow from the scar into the part they formerly supplied is shown by the fact that a tingling sensation, referred peripherally, can be provoked by tapping or firmly stroking the ulnar aspect of the proximal phalanx; a situation in which such growing fibres would be present.

Apart from the effect of the actual trauma of the nerve-fibres, which soon disappears, the burning sensation experienced for so long after the section of a nerve has no doubt a peripheral cause. We know that chromalytic changes are occurring in the sensory ganglion cells from which the severed fibres arise, and it might be thought that these changes could be the cause of the pain and hypersensitivity. But by pressing firmly with a finger of the right hand on the left ulnar nerve at the elbow, it was possible temporarily to prevent the passage of impulses along its fibres. If this were done, while the compression lasted the pain ceased to be felt; as soon as the pressure was released and the nerve-fibres had recovered from it, the pain reappeared. The cause is therefore peripheral.

Incidentally, I have endeavoured to determine whether severance of the nerves exerts any influence on the growth of the finger-nail.[1]

In order to test this I marked at the time of the first operation (on February 22) the base of the nail of the little finger on both hands with nitrate of silver. This marking has served to show that the nail of the operated finger has grown more slowly than that of the unoperated side. I have just cut away—in paring my nails—the silver marking of the normal side, so that this nail has taken five months to grow from base

[1] Langley found that some effect (of irregularity in growth) was produced after the nerve to one of his finger-tips had been accidentally torn.

to apex; the mark on the operated side is still 2 mm. from the apex. Further, on the operated side, there is a perceptible roughness of the nail across its width just at the level of the silver marking, showing that there was produced by the severance of the nerve some trophic disturbance in the growing nail.

Lastly, I may say a word about certain vascular changes which have been caused by the nerve severance.

In both fore-arms, although I could not assert that there was an increase in vascularity of the implicated area—it showed at any rate no perceptible difference of colour—there was produced a distinctly œdematous condition of the integument over the whole area. This was more pronounced on the cut side than on the squeezed side and soon disappeared altogether on the latter.[1] But on the cut side the condition remains as it was; and it has had the effect of increasing the apparent size of the fore-arm over the implicated area, so that when the two arms are placed side by side the left looks perceptibly larger than the right; the skin over the area is also smoother in appearance.

In the finger also there was and still is a decided change in the appearance of the integument. The whole finger is not larger than the normal one, if anything it is smaller. The skin looks smoother and feels harder; this is perhaps due to an œdematous condition. It also shows patches of white and red, as if the vessels were contracted over one part and dilated over another. But this is most apparent on the dorsal aspect of the little finger, and the nerves of this aspect are intact. It may be that the effect has been produced indirectly by tension due to œdema of the palmar integument.

What is very apparent is the relative *coldness* of the operated finger. One would have supposed that if the vascular nerves were severed—as they certainly must be on the radial side, and as they probably are on the ulnar side also—the skin of the finger would feel warm to the other hand or to the touch of another person; but the opposite is true, and this has been the case ever since the severance. This contrast in temperature between the operated finger and the normal is, even after five months, still striking.

The chief papers in which the subject of this communication has been previously dealt with are given below, but it is impossible to deal with them in detail in this résumé.

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[2] Head, Henry, and Rivers, W. R. *Brain*, 1908, **31,** 324.
[3] Trotter, Wilfred, and Davies, H. Morriston. *Journ. Physiol.*, 1909, **38,** 134; and *Journ. f. Psych. u. Neurol.*, 1913, **20,** 102.

[1] It may well be that all the fine vascular nerves were not fully severed by the squeeze.

DISCUSSION.

The PRESIDENT said that all present must have admired the courage and enterprise of Professor Sir Edward Sharpey Schafer in carrying out these observations upon his own limbs. Professor Stopford, however, who would open the discussion on Sensory Disorders later on, held views as to their explanation which were entirely different from those of Sir Edward Sharpey Schafer. Further, Sir Henry Head, whose classic observations on himself were the earliest of all, was unfortunately absent from the meetings, but Mr. Wilfred Trotter, who in conjunction with Mr. Davis had carried out extensive investigations on their own peripheral nerves many years ago, and had come to conclusions differing in some respects both from those of Schafer and of Head, was present. He would be glad, therefore, if Mr. Trotter would give his views.

Mr. WILFRED TROTTER said this subject lent itself to very discursive treatment, but he would attempt to be brief in his remarks. Few people have had experience of section of cutaneous nerves in their own body, and it is on that account a highly technical subject, and one which it was very difficult to present interestingly to those who had not, in their own persons, experienced the remarkable series of new sensations which occurred after section of a nerve and during recovery. He would on the present occasion confine himself to two remarks. In general he would say that Sir Edward Schafer's results corresponded with those which Mr. Morriston Davies and he got nearly twenty years ago after section of a large number of cutaneous nerves in one another. It occurred to him that an explanation of the results Sir Edward observed in his fore-arm was furnished by the experience Mr. Davies and he had in experimenting on the fore-arm. They found that there were three branches of what used to be called the internal cutaneous nerve of the fore-arm, and that section of the one which lay between the other two did not cause any anæsthesia at all. They cut the middle branch first, but it was not until the posterior branch was also divided that a substantial area of anæsthesia was produced.

The only other point he would mention, among the innumerable others which arose, was the question of recovery. Mr. Davies and he found that there was a distinct relation between the rate of recovery, the size of the nerve, and the density of its distribution. For instance, section at the knee of the internal saphenous, which is a long nerve but not a large one, produced a large area of anæsthesia on the inner surface of the leg, which recovered very slowly. The first nerve they divided was in the speaker's left leg, and even now, eighteen years after the operation, sensation has recovered incompletely, and there was still that hypersensitiveness to pain which represented the phenomenon called the "protopathic sensibility." On the other hand, in the case of the great auricular nerve, which is thicker but supplies an area only perhaps quarter the size of the internal saphenous, recovery was very much more rapid after section, and it became quite complete. This difference Mr. Davies and he attributed to the difference in the density of the nerve distribution, and some corresponding special degree of energy in regeneration. In connection with this point they

attempted, but failed, to establish statistically the density of the distribution of sensory nerves to the skin. It is an important matter, and of great interest, but it has never been done. They cut the piece of nerve removed transversely, and tried to count the number of its fibres, and relate it with the size of the area which was rendered anæsthetic. They were, however, unable to enumerate the axis-cylinders sufficiently exactly to justify any statistical conclusion. He is satisfied, however, that there was a gross difference in the number of the nerve fibres distributed to various parts of the skin, and, correspondingly, in the sensitiveness of the skin itself. It is possible to pick out relatively insensitive parts, as the inner surface of the cheek and the back of the fore-arm, where the sensitive spots are widely separated from one another. On the other hand, the tips of the fingers, the tip of the tongue and the surface of the face, are very richly supplied, and are correspondingly more sensitive. It would be of great value to theoretical neurology to obtain a statistical statement of the number of axis-cylinders per square centimetre distributed to various parts of the body.

He would also insist on the importance, in doing experimental work in this field, of knowing beforehand the distribution of the nerve which was to be cut. This could be determined exactly by stimulating the nerve with the faradic current before dividing it.

Sir EDWARD SCHAFER, in reply, said he had no idea of casting discredit on previous observations. The few experiments he had detailed were in no way comparable to the large number made by Davies and Trotter. He rejected, as they did, the theoretical deductions of Head and Rivers, without suggesting that the observations of these authors were incorrect. His main object in performing the experiments was to see the difference in the time of recovery of a nerve after squeezing and after cutting respectively. He suggested that if a surgeon wished to interrupt the course of a sensory nerve, it would be better to squeeze than to cut it, for after cutting full recovery of function might never be attained.

A subsidiary object was that he had to teach the subject, and he had found it difficult to explain to students what exactly happened in recovery; for this reason he determined to experiment on himself.

this factor need not be further considered here. Obstruction to the circulatory pathway is certainly the cause of clinical hydrocephalus in the vast majority of cases. Such an obstruction may be situated in the ventricular system, in the subarachnoid space, or may affect the arachnoid villi. It may be caused by neoplasms, various chronic and acute inflammatory conditions and, in early infancy, by developmental defects. The consequence of an obstruction in the ventricular system is a dilatation by the pressure of the retained fluid of that portion of the system which lies proximal to the lesion. From the above considerations it is clear that the term *unilateral hydrocephalus* should be restricted to cases in which one lateral ventricle or a part of it becomes dilated by reason of an obstruction affecting its cavity or its outlet. It is well known that in diseases of the central nervous system associated with atrophic shrinkage of the cerebral hemispheres the lateral ventricles become passively enlarged. Hydrocephalus in its present clinical significance is a misnomer as applied to this condition in which the accumulation of fluid is not injurious but is, on the contrary, beneficial in so far as it maintains normal pressure conditions within the skull. It is equally incorrect to apply the term unilateral hydrocephalus to cases in which a local atrophy of brain substance has caused a corresponding enlargement of one lateral ventricle or a part of it.

Most of the records of "unilateral hydrocephalus" which I have been able to collect are concerned with cases of this nature [1, 2, 3, 4, 5]. In a few instances there is some doubt as to the exact nature of the case, but there are strong reasons [1] to believe that they were not of an obstructive nature [6, 7, 8, 9]. Ziegler, in his "Textbook of Pathology," 1881 [10], says that in unilateral hydrocephalus the foramen of Monro has been found closed in a few cases, but he gives no details nor references.[2] Since Dandy [11] published his account of the production of experimental unilateral hydrocephalus by operative occlusion of one foramen of Monro, it has become customary for those writing on the

[1] Spiller thought his case might be due to obstruction, as there were some nodules of gliosis which *partially* encroached on the foramen of Monro. The patient was a congenital hemiplegic idiot, there were gross degenerative changes in the brain, the cranial chamber on the affected side was actually smaller than on the less affected side, and there had been no symptoms pointing to increased intracranial pressure. Obviously the case was not one of obstructive hydrocephalus. In the other records quoted the state of the foramen of Monro is not mentioned, but the necropsy and clinical data given leave no doubt that they were cases of localized cerebral degeneration.

[2] Rivarola (Bol. y Trab. de la Soc. cirug. de Buenos Aires, 1922, vi, 771-774) reports a case under the title "A propósito de una enferma de hydrocephalia univentrécular," but I have been unable to consult his paper.

A CASE OF LEFT UNILATERAL HYDROCEPHALUS IN AN INFANT. OPERATION—CURE

BY NORMAN M. DOTT.
(*Edinburgh.*)

THE literature concerning "unilateral hydrocephalus," though scanty, is much confused by the application of this term to essentially different conditions. It has been applied on the one hand to cases in which one lateral ventricle has been actively distended by reason of obstruction to the escape of cerebro-spinal fluid from it, and on the other hand to cases in which one lateral ventricle has become passively enlarged by reason of local atrophic shrinkage of the adjacent brain substance. In this connection a few words concerning the definition of hydrocephalus and its unilateral variety may not be amiss before proceeding to a description of the case which forms the subject of this communication.

"Hydrocephalus" of course means water in the head, and being applied to a pathological clinical state it further implies that the water is in excess and is of pathological significance. It is essential that the term be restricted to conditions in which the excess of "water" is an actual cause in whole or in part of the patient's symptoms. The cerebro-spinal fluid can of itself be injurious in only one way, namely, by exercising an undue pressure on the surrounding tissues. *Hydrocephalus* may, therefore, be defined as *an excessive accumulation of cerebro-spinal fluid under excessive pressure.*

The cerebro-spinal fluid is produced at a considerable secretory pressure by the choroid plexuses. It circulates through the ventricular channels and sub-arachnoid spaces, and leaves the latter by entering the venous sinuses of the dura mater by way of the arachnoid villi. An excessive accumulation of this fluid under excessive pressure may be caused in only two possible ways—obstruction to its circulation, or an abnormal increase in its secretion. Increased secretion probably plays little or no part in clinical hydrocephalus. The natural outlets for the fluid are very free, and it is difficult to conceive of an increase of secretion so great as to cause definite hypertension unless the circulatory pathway were obstructed. It is quite obvious that excessive secretion could not possibly cause a localized hypertension in one ventricle, and hence

There is a definite right hemiparesis. The right angle of the mouth is weak; the upper part of the face moves symmetrically. The right arm and fore-arm are slightly thinner than the left. Attempts to grasp objects are clumsy and weak with the right hand and natural with the left. The weakness is most marked in the hand, but is present at elbow and shoulder. The biceps, triceps and supinator-jerks are markedly increased in the right arm and natural in the left. The lower extremities appear symmetrical. On such movements as drawing the legs up, the right limb always lags behind the left. No gross weakness can be made out. The knee and ankle-jerks are markedly exaggerated on the right and natural on the left. The Babinski sign is positive on each side (normal in infants). The right abdominal reflex is absent, the left present.

There is a complete, clean-cut, right homonymous hemianopia. This was first noted by the ward sister, who observed that on approaching the child from the left side she at once looked round, while approaching from the right was not noticed. The defect was afterwards verified easily and convincingly at repeated examinations, the usual method of testing against the observer's own field being employed. The test objects were pieces of white paper of varying size. The patient's recognition of the moving object at the periphery of the visual field was immediately signalized by fixation of vision upon it. In this way the fields could be measured with a considerable degree of accuracy.

Provisional diagnosis.—It was quite obvious that the chronic hydrocephalic process affected mainly the left cerebral hemisphere, as indicated by the greater distension of the left half of the skull and the right hemiparesis and hemianopia. The only possible explanation was left unilateral hydrocephalus, due to a permanent obstruction. The exact site of the obstruction and its nature were still uncertain.

Ventricular puncture (February 21, 1927).—The left lateral ventricle was tapped through the lateral angle of the anterior fontanelle, and 10 c.c. of fluid withdrawn. The fluid was faintly xanthochromic. It contained eighteen lymphocytes per c.mm.; there was an enormous excess of protein, so that the fluid became semi-solid on the addition of a few drops of alcohol. These findings indicated stasis of the fluid.

One c.c. of neutral phenolsulphonephthalein was injected into the left ventricle. The fluid obtained by lumbar puncture thirty minutes later contained no dye, nor did the urine collected during three hours after the injection. Two days later the left ventricle was again tapped and the fluid obtained was still strongly coloured by the dye. These findings indicated that the cavity did not communicate with the subarachnoid space. The exact site of the obstruction was still uncertain.

Ventriculography (February 28, 1927), by Mr. A. J. C. Hamilton.—The left lateral ventricle was again tapped, and the fluid slowly replaced by oxygen until 100 c.c. of fluid had been withdrawn, and 80 c.c. of oxygen injected. Stereoscopic radiograms were now taken (see figs 1 and 2). They showed

subject of chronic hydrocephalus to cite a pathological obstruction at this situation quite familiarly as one of the causes of the disease. I have, however, been able to discover only three recorded cases of undoubted unilateral hydrocephalus in the proper sense of the term. Two [12, 13] were cases of pedunculated intraventricular tumour in adults which caused intermittent acute hydrocephalus by an intermittent "ball-valve" closure of the foramen of Monro. One [14, 15], also in an adult, was due to tuberculous masses and adhesions obstructing the inferior horn of a lateral ventricle, which caused a progressive hydrocephalus affecting the obstructed horn.

The case which I shall now describe appears to be the first of its kind to be recorded. It was that of an infant in which the left foramen of Monro was obliterated by scar tissue, causing a progressive left unilateral hydrocephalus. The condition could be quite definitely diagnosed, and it proved amenable to surgical intervention.

E. P., female, 9 months, was admitted to Royal Hospital for Sick Children, Edinburgh, February 15, 1927, and discharged June 3, 1927.

The baby is the youngest of a family of thirteen. No history of left-handedness in family. Birth was natural and easy. The first five months of infancy were quite uneventful. Especially no febrile attack, neck stiffness, nor even undue irritability were observed. (The mother is quite intelligent, careful and experienced.)

History of present illness (obtained March 12, 1927, from mother).—Five months ago: Commencing enlargement of head, which had steadily progressed to date. Dilatation of veins about outer angles of orbits. Four months ago: Since this time to date the child has not slept well and has been cross and irritable. Three months ago: Deficiency in prehension and grasp of right hand, which has been slightly progressive to date. Two months ago: A defect of vision, which parents could not understand and cannot describe; it persists to date. Two months ago: Since this time there has been occasional recurrent internal strabismus; it is not clear which eye was affected.

Examination.—The child is of normal proportions for her age, with the exception of the enlarged head. The complexion is sallow, and varies frequently from extreme pallor to faint pink. The musculature generally is soft and flabby. The temperature varies frequently between 98° and 100° F., with corresponding alterations in the pulse-rate. The blood Wassermann reaction is negative (January 19, 1927). Routine examination reveals no abnormalities beyond those of the nervous system recorded below.

Positive neurological findings.—Notable and asymmetrical enlargement of head. Greatest circumference, 51·5 cm.; left side, glabella to external occipital protuberance, 28·5 cm.; right side, 23 cm. Slight left proptosis. The fontanelle is very wide, bulging and tense; the cranial sutures are widely separated and the bones mobile.

of preserved specimens of hydrocephalic brains, and my house-surgeon, Dr. J. C. Gillies, impressed by their appearance, suggested that an aperture might be made through the septum lucidum. This appeared to us a simpler procedure than excision of the choroid plexus. The plan of operation decided on was either to excise the plexus or make a window in the septum lucidum, according as which appeared more feasible at the time. The latter procedure was actually adopted.

FIG. 2.—*Ventriculogram* (one of stereo-pair). Position: right side of head uppermost. When viewed stereoscopically the collection of oxygen can be seen to be in middle of head, i.e., it lies against mesial wall of left ventricle, being unable to pass into uppermost right ventricle. Note distinct outline of excessively arched corpus callosum.

Operation (March 14, 1927).—The scalp in the left parietal region was infiltrated with ½ per cent. novocain solution to which a few drops of adrenalin had been added. This anæsthesia proved entirely satisfactory, and the baby took a normal feed with avidity at intervals during the operation. The operation occupied about one hour. The child's condition, which was supervised by Miss W. Wood, did not give rise to anxiety at any time.

A straight sagittal incision was made just below the left parietal eminence. The skull was perforated and the opening enlarged to 3 by 4 cm. After reducing tension by tapping the ventricle, the dura was opened to the bone margins by a

an enormous dilatation of the left lateral ventricle, which occupied almost half the cranium. The outline of the corpus callosum and septum lucidum, deviated considerably to the right, could be clearly seen. There was now no doubt that the entire ventricular cavity was involved, and that the obstruction lay at the left foramen of Monro. The ontline of the ventricle was smooth at this situation, and the marked deviation of mid-line structures to the right rendered a mid-line tumour unlikely. A chronic inflammatory process other than syphilis appeared the most probable pathological cause.

FIG. 1.—*Ventriculogram* (one of stereo-pair): 80 c.c. oxygen in left lateral ventricle. Position: left side of head uppermost. Observe approximately globular form of enormously distended left lateral ventricle.

Treatment.—The obvious plan of re-establishing normal conditions by reopening the foramen of Monro appeared impracticable. It would be impossible to make a large opening here without inflicting undue damage, and if, as expected, scar tissue were the cause of obstruction, an opening through it would not be likely to remain permanent. Dandy [16] has shown experimentally that when the foramen of Monro is obstructed and the choroid plexus of the same side completely excised, the ventricle does not become dilated, but actually collapses. Excision of the choroid plexus appeared a possible line of treatment. In considering the problem we examined a number

cruciate incision. The exposed cortex was pale and avascular, and convolutions were hardly recognizable. The lepto-meninges were not thickened. After securing one cortical vein with silver clips, a vertical incision was made into the ventricle. The brain substance in this area was only 6 or 7 mm. thick. The margins of the incision were immediately wrapped in moist cotton wool and retractors inserted, as shown in fig. 3, to avoid collapse of the thin brain substance which would have obscured the view. The ventricle contained turbid brownish fluid (old retained hæmorrhage from previous punctures), which was rapidly evacuated by the suction apparatus. With the aid of the headlight the enormous cavity could now be inspected throughout. The details observed are shown in fig. 4. The entire surface was smooth and glistening and of a dirty yellow colour. The impression was that given by a yellowish glaze on white porcelain. The texture of the surface was strongly reminiscent of an old, organized pleurisy. The surface was quite uninterrupted at the foramen of Monro, the site of which was indicated only by the veins from the thalamus and caudate nuclei converging upon it. The choroid plexus was buried in the organized tissue which lined the ventricle. Its outline could be distinguished as a purplish streak, but the ventricular surface over it was quite smooth. Its excision was obviously out of the question. The appearance suggested that it must be practically functionless.

The outline of the corpus callosum and, just beneath it, the septum lucidum were easily distinguished. The septum was penetrated by a minute hooked knife, and through the aperture perfectly clear fluid flowed from the right ventricle—in marked contrast to the brownish fluid which the left ventricle had contained. The septum was unexpectedly tough and vascular, being of leathery consistence, and containing numerous engorged veins. The latter had to be secured before division by silver clips, while the septum had to be cut with sharp, strong scissors. In this way a large aperture, about 20 by 15 mm., was cleanly cut in the septum. Through this window a limited view of the normal right ventricle was obtained. The pure whiteness of its walls was in marked contrast to the dirty yellow of the obstructed left ventricle. A part of the normal right choroid plexus could also be observed floating freely in the clear fluid. When the cavity was dried out, drops of clear fluid could be seen exuding from the surface of the actively secreting plexus. A free drainage having thus been established for the dilated left ventricle, its cavity was washed out with Ringer's solution to remove all traces of blood, and it was then filled completely with the same fluid.

The cortical incision was not sutured, as it always closes rapidly even in hydrocephalus. The dura was carefully and completely closed. The scalp was closed as usual in two layers of fine, silk sutures applied to the galea aponeurotica and skin edges respectively.

As will be seen from fig. 3, the left ventricle now drains into the right through the opening in the septum lucidum. The normal right foramen of Monro provides an exit for the secretions of both lateral ventricles.

Convalescence.—An early post-operative hyperthermia was controlled by cool

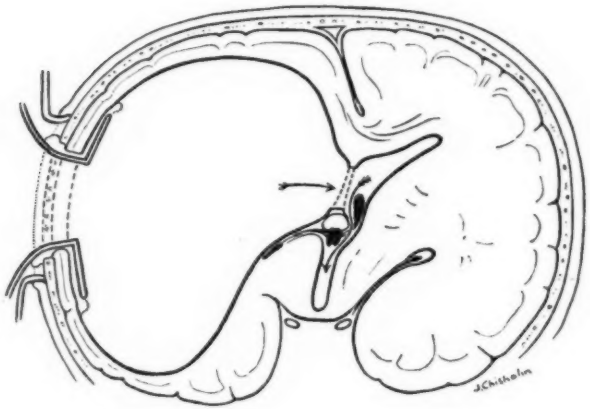

FIG. 3.—*Sectional diagram indicating method of operative procedure.*—Note the retractors holding the thin cortex out against the skull. The part of the septum lucidum which was resected is indicated by dotted lines. The arrows indicate the new drainage pathway made for the obstructed left ventricle, viz., through the septum lucidum into the normal right ventricle, both cavities draining through the remaining right foramen of Monro.

FIG. 4.—*Drawing of appearances seen at operation.*—Observe the large, smooth, ovoid cavity, the temporal horn being partially obliterated. The outlines of corpus callosum, thalamus, occipital and temporal radiations can be appreciated. The veins converging on the site of the obliterated left foramen of Monro are seen. The choroid plexus is buried in scar tissue. The aperture cut in the septum lucidum reveals the normal choroid plexus and upper surface of thalamus in the right lateral ventricle. Note silver clips securing veins at cut edges of aperture.

sponging and exposure, and subsided after twenty-four hours. Thereafter recovery was uneventful. Intracranial fluid pressure, as judged by the fontanelle, fell gradually during the first week, when the fontanelle had become quite concave.

10th day.—The head has diminished by 1 cm. in circumference, 50·5 cm.

12th day.—The child is now beginning to use her right hand to steady feeding bottle, etc.

23rd day.—The head now measures 49·5 cm. The shrinkage has occurred chiefly in the antero-posterior axis, the fontanelle diminishing in length and the bones overlapping slightly at the coronal sutures. The fontanelle remains slack and concave.

FIG. 5.—*Photograph of patient six weeks after operation.*—Observe concave fontanelle (which has greatly diminished in size) and prominences at coronal sutures due to overlapping of the bones as the skull attempts to shrink.

30th day.—No facial weakness is now apparent. She uses the hands with equal freedom, though the right is still a little weak and clumsy. The tendon reflexes are symmetrical throughout. The hemianopia persists unaltered. General condition fairly satisfactory, though she remains rather sallow and flabby and has not gained weight.

80th day.—The skull measurement remains 49·5 cm., the skull having apparently shrunk as far as is possible. The fontanelle and operative site remain depressed (see fig. 5). Neurological findings as above. General condition improving, has gained some weight.

July 11, 1927—four months after operation.—She has been very well, has gained over 3 lb. in weight and has cut two teeth. She is now a bright,

lively child, takes interest in all her surroundings and plays with toys. She has learned to say a few words quite clearly; she repeats these by imitation, though she does not yet make use of speech to ask for her wants, etc. (15 months old). There is now no trace of weakness in the right hand, and she uses the arms and hands equally well. She can stand and walk a few steps; the legs are used with equal freedom. The tendon reflexes are normal and symmetrical throughout. The abdominal reflexes are present and equal. Hemianopia is still present, though the impression is gained that it is not now

FIG. 6.—*X-ray* (Dr. Woodburn Morison, Royal Infirmary, Edinburgh), *six weeks after operation.*—Observe operative opening in skull, O; group of silver clips on septum lucidum, SL; two clips on shrunken cortex, C; and a clip on a meningeal artery in the dura, D.

absolute when large objects are used. The fontanelle is almost closed. The intracranial tension is still low, the site of the operative bone defect being concave and pulsating freely.

To this date, then, the hydrocephalus is cured. The hemiparesis has completely recovered. Speech by imitation is quite good for her age. Hemianopia persists, though acuity of vision is probably unaffected. This degree of recovery is surprising considering the condition of the left cerebral hemisphere at the time of operation. It is not yet possible to estimate accurately the intellectual

capacity, but there is no suggestion of intellectual defect, though such deficiency can often be recognized in patients of her age.

Pathology.—The portion of the septum lucidum excised at operation was immediately fixed in Zenker's fluid and subsequently sectioned in the coronal plane (see fig. 7). The ependyma forming the wall of the right ventricle is normal. The substance of the septum shows an extreme gliosis with marked thickening and with obliteration of its cavity. The surface which formed part of the wall of the distended left ventricle is covered by a layer of organized, fibrous scar tissue. The ependyma has been almost completely destroyed and only a few clusters of buried and degenerative ependymal cells are seen.

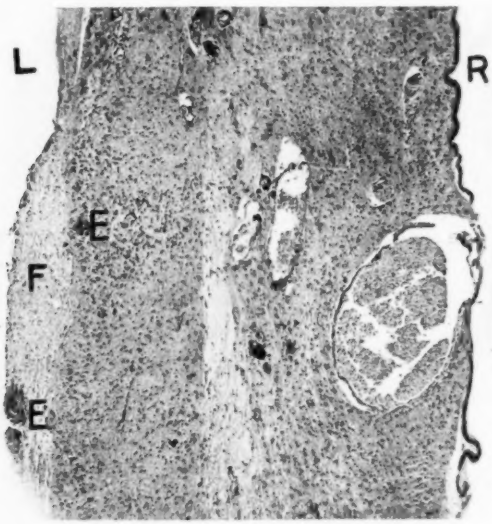

FIG. 7.—*Microphotograph* (Mr. Tom Hamilton, Royal College of Physicians Laboratory, Edinburgh) × 15, *of coronal section through resected portion of septum lucidum.* (Zenker, Azan-Mallory.)—There is general gliosis with obliteration of cavity of septum. The right surface, R, is clothed by a layer of normal ependyma. The left surface, L, is covered by a layer of organized, fibrous scar tissue, F, with here and there groups of buried and degenerative ependymal cells, E. The veins are greatly dilated.

From the smooth and continuous appearance of the left ventricular wall at operation, it is certain that the entire wall was of the same nature as that shown by the septum—it was lined by a layer of organized, fibrous scar tissue, which had also obliterated the foramen of Monro.

In the above case there was a chronic left unilateral hydrocephalus of at least four months' duration, due to scar tissue obliterating the left foramen of Monro. The scar tissue was obviously the consequence of a

previous inflammatory condition which had been localized to the left lateral ventricle.

A sudden complete obstruction at the foramen of Monro is a rapidly fatal condition, as illustrated by the case reported by Batten and Collier [17], in which a simple cyst of the choroid plexus became impacted in this situation. Both foramina were obstructed by it and death occurred in fifteen days from the extremely rapid distension of the lateral ventricles. Sir Thomas Fraser [18] has reported a similar case. In my patient the comparative chronicity of the disease, in spite of a complete obstruction, is explained by two factors. The patient was a young infant with a distensible skull, and the choroid plexus of the obstructed ventricle was severely damaged by the initial inflammatory lesion and must have produced much less fluid than a healthy plexus.

In the absence of more definite data concerning the original lesion, a decided opinion as to its cause cannot be given. The characteristic fibrous scar tissue which lined its walls and buried its choroid plexus can leave little doubt that it was a severe inflammation of infective origin which was localized to the left ventricle. That hydrocephalus may follow these lesions by reason of scar tissue obstruction in the ventricular system is borne out by an extensive literature on the subject. The site of obstruction is usually the roof of the fourth ventricle, or more rarely the aqueduct of Sylvius [19]. Dupérié [20] records an interesting example which probably illustrates a case of this nature. He mentions particularly that, when the inflammatory process is confined to the ventricles and does not involve the meninges, the clinical symptoms are very slight and obscure. In my case the mother noted no acute symptoms at or before the onset of hydrocephalus. His patient, an infant of four months, had a progressive hydrocephalus of two months' duration. The fluid from lumbar puncture was quite normal; that from "the ventricle" was turbid, xanthochromic, and contained a great excess of cells and protein. No organism was found. The ventriculitis was thought to be due to septicæmia from a previous attack of gastro-enteritis. It is clear that in this case an active infective process had become localized and shut off in the ventricular system. There had never been symptoms suggestive of meningitis, and it is probable that the infective process became early shut off by inflammatory closure of one of the narrow intracerebral passages, and the meninges had never become infected. This, I believe, was the course of events in my patient.

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DISCUSSION.

Dr. Bernard Sachs said that, from his knowledge of the literature of the subject which he had gone over carefully, unilateral hydrocephalus was very rare. Therefore, when a case of that sort presented itself, the difficulty of diagnosis would be unusually great. One would be apt to suspect early meningeal processes, or possibly a latent tumour giving rise to the unilateral hydrocephalus. Mr. Dott was fortunate in this case in that he had managed to bring about a favourable result; the speaker doubted whether many would be able to record similar successes. Was the child now progressing normally?

Dr. E. Sachs remarked that Mr. Dott put dye into one ventricle and failed to recover any in the spinal canal; did he put dye into the other ventricle, and, if so, did he then recover any? If the right ventricle was normal, there should have been no obstruction. He asked what was the shape of the opposite ventricle, and whether Mr. Dott attempted to put air into the opposite ventricle? That would have been necessary before establishing positively that it was unilateral hydrocephalus.

With regard to ætiology, he had seen one case which might throw some light on this point. A child sustained a birth injury, and probably had a cerebral hæmorrhage. He did not operate on the child, but kept in touch with it, and after several months it developed internal hydrocephalus, and the fluid in the ventricles was similar to the fluid Mr. Dott described, yellow, with flocculi in it. Possibly in Mr. Dott's case the condition may have been due to a birth injury and hæmorrhage.

Dr. ALFRED TAYLOR said the only case he had seen in which there appeared to be a unilateral hydrocephalus turned out to be porencephaly of the left hemisphere which communicated with the posterior part of the lateral ventricle. The child died shortly after operation.

Mr. DOTT, in reply, said the child was now progressing well. He did not put dye or air into the right ventricle, as he wanted to limit his procedure to the minimum which would supply him with the information he required. That the dye was not recovered from the urine after injection of it into the left lateral ventricle showed that the dye was confined to the ventricular system. Oxygen was put into the left lateral ventricle and the head was so turned that the right lateral ventricle was uppermost, and if the foramen of Munro had been patent the oxygen would have passed into the right lateral ventricle. As it did not do so, he knew the foramen was blocked. He thought in this case the cause was inflammatory; the gross amount of scar tissue, like that in an organized pleurisy, which lined the ventricle proved that definitely.

CEREBRO-CEREBELLAR AGENESIS IN ITS RELATION TO CEREBELLAR FUNCTION.

BY LEON HASTINGS CORNWALL, M.D.
(*New York.*)

FOR the material on which this report is based I am indebted to Dr. Stanley Cobb, of Boston, Massachusetts. It consisted of a kitten that showed evidence from birth of pronounced neural defects referable to the kinesthetic and kinetic regulatory systems. The animal was sent to Dr. Tilney by Dr. Cobb in the summer of 1926, and after several weeks of observation, during which moving picture records were made, the animal was killed at the age of two months. At the request of Dr. Tilney I undertook the pathological investigation. This was made under his supervision, and for his helpful guidance and many suggestions I take this occasion to express my grateful appreciation.

Dr. Cobb was good enough to obtain from the erstwhile mistress of this kitten a very satisfactory life-history, together with data concerning the mother and maternal grandmother. I shall include this verbatim as it is a tribute to the observational acuity of its author.

"Here are the only facts that I know about the tumbling kitten. We got his grandmother at Harvard, Massachusetts, in 1924, from a good stock of black cats. She was born June 3, 1924, and was a fine cat, intelligent, affectionate and a clever mouser.

"On May 2, 1925, she had four kittens. Two were all black, like herself, and two were fine Maltese. They were all healthy and flourishing. We named one of the black females Nicolette, a nice, clean, affectionate and intelligent cat. On April 24, 1926, Nicolette had four kittens. One, which was born dead, was very much underdeveloped, in fact hardly more than a well-defined embryo. The second, a golden-yellow male, died in two days. The third, a golden-yellow female, was very lively, bright and healthy. We still have her. The fourth was the greyish mongrel male that I took to the laboratory. He was lazier than the female, and opened his eyes two days later, almost ten days after birth. He was also very fat and greedy, and was always first to nurse and last to stop, pushing his sister away. His laziness and fatness seemed at first sufficient cause for not walking or climbing as his sister did. At almost four weeks it was plain that he could not support himself on his legs. He would roll and pull himself across the room to his mother, resting now and then on his back and waving his paws aimlessly in the air. His mother kept away from him.

"As soon as the normal kitten could climb in and out of their low basket, the mother would lie out on the floor of the room and let it come to be nursed. The male kitten was unable to climb the three-inch barrier, and unless I lifted him out and gave him to his mother she would not nurse him, but she washed him carefully and whimpered over him often. He was gay and happy, purred loudly when stroked, and tried to play with his more active sister. If I supported his chest he would try to lap, but unsupported he took a nose-dive into the saucer. He was so placid and even-tempered that we thought he might be blind, but to flash-light he blinked normally, so we decided that he was able to see though he did not react quickly to dangling strings or other playthings."

Up to the time of death the kitten was never able to maintain normal physiological postures. It made attempts to stand but in the effort would fall forward on its nose, or to one side. It succeeded in pulling itself along slightly while lying on its side. While in the latter position it was able to use the fore-legs, in a well co-ordinated fashion, to play with articles that were dangled before it or placed on the floor near it. In these playful manœuvres the head and neck movements were well co-ordinated. The head required support when the animal was given milk, otherwise its nose would forcibly hit the bottom of the dish and then be withdrawn quickly, due to the asynergia of the neck musculature. Lateral movements of the head and neck were executed with but slight evidence of inco-ordination.

When placed in a tub of water the animal first assumed a position on its back. Efforts to keep its nose out of the water were not successful, and the animal had to be removed to prevent drowning. After an interval of ten minutes, the animal was thrown into the water a second time, and on this occasion was much more successful in the efforts to keep its nose out. In doing this vigorous use was made of all of the axial and appendicular musculature, and the result was a circus movement.

The pupillary reactions to light were prompt, and no spontaneous nystagmus was observed. On douching the ears with hot water, nystagmus was promptly induced with the rapid components toward the side stimulated. With cold water the nystagmus consisted of slower oscillations with less amplitude than was produced by hot water, and the differentiation between the rapid and slow components was much less marked, but the movements were slightly more rapid to the side opposite that stimulated. The patellar and ankle jerks were present on both sides.

The clinical features indicated clearly severe defects of the kinetic and kinesthetic mechanisms, both in the static phase concerned with the posture and equilibrium, and in the dynamic phase concerned with synergized movement and locomotion.

An examination of the brain disclosed that the cerebellum was reduced in all of its dimensions, but more so in the antero-posterior direction than transversely. As a control the brain of a normal sixty-two day kitten was used. In the normal animal the antero-posterior measurement of the cerebellum was 15 mm. as compared with 8 mm. in the pathological animal, a difference of

olives and to the emergent fibres of the twelfth nerve, occupied by the uncrossed fibres of the Deitero-spinal tract, was pale and lacking in normal definition; it was estimated to be about one-fifth to one-tenth of the normal size for an animal of this age. The longitudinal bundles in the formatio reticularis were paler and more poorly defined than in the control animal. The deficient myelinization of the dorsal and ventral spino-cerebellar tracts was reflected in the restiform bundles, which were pale in the peripheral zones but possessed well-stained core bundles.

The myelinized fibres in the grey matter were less numerous, more delicate and smaller than in the control animal. There were many bulbous and bead-like swellings of the myelin. This was especially noticeable in the decussating fibres dorsal to the central canal.

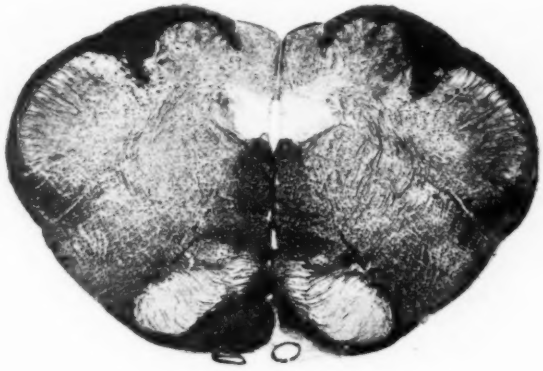

FIG. 2.—Section through the myelencephalon at the caudal extremity of the inferior olive. Note the reduced size of the right pyramid, the number and delicacy of the internal arcuate fibres, the relative absence of external arcuate fibres, the deficiency of the dorsal and ventral spino-cerebellar tracts, the delicacy of all fibre constituents in the grey matter, and the reduced size and paleness of the longitudinal bundles in the formatio reticularis.

The eighth, ninth, tenth, eleventh and twelfth nerves were all smaller and less densely stained than those of the control animal. The fasciculi were smaller and the fibres more delicate. The cochlear division of the eighth was slightly smaller on the right than on the left side.

The measurements of the inferior olives in their cephalocaudal diameters showed a reduction of about 25 per cent.; this measurement was 4 mm. as compared with 4·7 mm. in the normal animal. The lateral diameters of the inferior olives did not show any variation from the normal and were equal on the two sides. Attention was also given to measurements of the several constituents of the olives, and approximately the same ratio obtained for the individual constituents as for the whole structure.

nearly two to one. In width the normal cerebellum measured 17.2 mm. and the pathological 16 mm. In addition to the cerebellar aplasia there was also a defect of the right frontal and parietal areas in the vicinity of the Sylvian fossa.

After fixation in Müller's fluid for several weeks, the brain was imbedded in celloidin, and serial sections, 50 microns thick, were cut from the level of the nuclei gracilis and cuneatus to the tips of the frontal lobes, and every fifth section was stained by the Kulschitsky modification of the Weigert-Pal method.

FIG. 1.—Superior surface of the brain and spinal cord showing the defective development of the right cerebral hemisphere and the diminutive cerebellum.

Myelencephalon.—The most striking feature was the almost complete absence of the pyramidal tract on the right side. Lissauer's zone, the fibres of the dorsal columns, the spinal fifth, the rubrospinal tracts and the fasciculus longitudinalis posterior, were well stained.

The internal arcuate fibres were easily seen, but they were less numerous and finer than in the control animal. The external arcuate fibres were few in number and were distinguished with difficulty. On both sides the ventro-lateral peripheral zone, occupied by the dorsal and ventral spino-cerebellar tracts, was very pale and contained only a small number of myelinated fibres. The right side was slightly paler than the left. The area just lateral to the

loosely arranged fasciculi. The acoustic tubercles were smaller on both sides than in the control animal, and appeared slightly smaller on the right than on the left side.

The sixth and seventh nerves showed no variation from the control animal. The mesial and lateral cell masses of the cerebellum did not appear much, if at all, reduced in size, but the deficiency of the fibre constituents that normally circumscribe them left them without definitive outlines. The lateral nuclear mass, comprised of the dentatus and emboliformis, measured 3·5 mm. in its longitudinal (cephalo-caudal) diameter, which was the same as the normal animal. The mesial nuclear mass, consisting of the fastigius and globosus, measured 2·5 mm. cephalo-caudally as compared to 2·75 mm. in the normal.

FIG. 3. —Section through the myelencephalon at the cephalic extremity of the inferior olive.

(Table I). The decussation over the nuclei fastigii consisted of merely three or four bundles of fine fibres. Several large lacunæ were present in the lateral nuclear group.

All of the core bundles of the cerebellum were small, poorly stained, and comprised of fine, delicate fibres. The uvula consisted of three poorly differentiated folia. The paraflocculus appeared as a very primitive structure that could not be differentiated from the tonsil. Both crura of the lobulus ansiformis were rudimentary and faintly stained. The paramedian lobes were faintly stained, lacking in structural differentiation and consisted of three folia.

The central core of the pyramis was more deeply stained and consisted of denser fibres than any other portion of the cerebellum. The largest fibres of the middle peduncle could be traced to the vicinity of the pyramis and supra-

These measurements are shown in Table I. The terminology of "fish old" for the mesial portion, "bird old" for the dorso-mesial portion, and "mammal old" for the chief or intermediate portion, was suggested by Dr. Frederick Tilney in a personal communication concerning some of his as yet unpublished studies on the comparative morphology of this structure. These terms have a connotative significance that justifies their use. It should be noted that the chief, or neo-olive, which is the mammalian contribution to the evolution of this structure, is more deficient than either the mesial or the dorso-mesial portion, which together constitute the paleo-olive.

The olivary convolutions lacked the sharp outlines seen in the normal animal. The borders were irregular, crenated and lacking in the rotundity so characteristic of these structures normally. The lack of definition of the inferior olives was due in part at least to the reduction of the size of the core bundles and the circumscribing fibres, but in addition to this there was disorder in the arrangement of the cells of the olivary cortex.

TABLE I.—PLANOMETRIC MEASUREMENTS OF THE PRE-CEREBELLAR AND INTRA-CEREBELLAR NUCLEI, CEREBELLUM AND JUXTA-RESTIFORM BUNDLES.

	Pathological	Normal
Pre cerebellar nuclei (longitudinal dimensions):		
Mesial or "fish old" olive	4·0 mm. ..	4·7 mm.
Dorso-mesial or "bird old" olive ..	3·75 ,, ..	4·0 ,,
Chief or "mammal old" olive	1·5 ,, ..	2·0 ,,
Schwalbe's area	3·0 ,, ..	4·5 ,,
Deiters' area	5·0 ,, ..	5·0 ,,
Intra-cerebellar nuclei (longitudinal dimensions):		
Mesial (fastigius and globosus)	2·5 ,, ..	2·75 ,,
Lateral (dentatus and emboliformis) ..	3·5 ,, ..	3·5 ,,
Cerebellum:		
Longitudinal dimensions	8·0 ,, ..	15·0 ,,
Transverse dimensions	1·6 ,, ..	1·72 ,,
Juxta-restiform bundles:		
Longitudinal dimensions	1·5	2·75 ,,

Metencephalon.—The juxta-restiform bundles disclosed the most striking pathological features. Their cephalo-caudal measurement was 1·5 mm. as compared with 2·75 mm. in the normal animal. The definition of these structures was very poor, and the fibre bundles were small in size and greatly reduced in number. The bundles that were present were very pale as compared with deeply stained and dense corresponding structures in the normal animal.

The areas occupied by the nuclei of Deiters and Schwalbe were measured. Deiters' area showed no variation in size from the normal, in each case the cephalo-caudal diameter was 5 mm. The cerebellar fibres emerging from Deiters' area were, however, very pale and grouped into small bundles that were fewer in number than in the normal animal. Schwalbe's area measured in its cephalo-caudal extent 3 mm. as compared with 4·5 mm. in the normal. (Table I.)

The superior olives were poorly defined and the fibres leading from them were reduced in number and size. The myelinized fibres originating from the medullary centres of the superior olives consisted of a small number of

cellular structures consisted of small, round, deeply stained nulcei (microglia), larger round and cuboid nuclei with less dense chromatin (oligodendroglia) and still larger nuclei resembling in size those of protoplasmic and fibrous glial astrocytes. The ventricle was dilated and the lining ependymal cells were either entirely lacking or arranged in rows of from four to eight cells. The latter picture was more frequently seen. In many localities the ependymal cells were grouped in clusters forming irregular nodular masses. Beneath the ependyma there were isolated groups of densely arranged small, round, deeply staining cells that were disposed parallel to the ventricular wall. At the tips of the ventricles these cellular masses extended out towards the periphery as finger-like prolongations.

In the left cerebral hemisphere the same condition obtained, but in lesser degree. The centrum hemi-ovale contained many corpora amylacea surrounded by a dense mass of glial cells and fibres and many young capillaries. The ventricle was not dilated as on the right side, but the ependyma was heaped up and consisted of several layers of cells with many ependymal granulations. In contrast to the right side there was a fairly broad strip of myelinized fibres, but this was less than in the normal animal. In the cortex and subcortex of both hemispheres glial nuclei were more abundant than normally and rod cells were present in all of the laminæ.

There was no perivascular infiltration in any portion of the cerebrum, nor was there any cellular exudate into the spaces of the pia-arachnoid. The pia appeared normal but the arachnoid was thickened in some areas. The blood-vessels showed no pathological changes.

No detailed study of the cellular structures was possible because of the preliminary fixation with Müller's fluid and the thickness at which the sections were cut. There appeared to be, however, a superabundance of glia nuclei in the grey matter of the medulla oblongata, and the cells of the ventro-mesial and ventro-lateral groups in the upper cervical region and medulla oblongata appeared to be reduced in number and size. Although the number of cells in the nucleus hypoglossus, nucleus ambiguus, nucleus dorsalis of the tenth and the nucleus of the fasciculus solitarius compared favourably with the control animal, their size was diminished.

The cells of the inferior olives were small in size and there was complete absence of any orderly arrangement. This same feature was noted in all parts of the cerebellum—the differentiation into molecular, granular and medullary layers being almost entirely lacking. In a few localities scattered groups of granular cells could be distinguished; they were very small and intermingled with them in a disorderly manner were some Purkinje cells. In the lobus biventer and the central folia of the pyramis the granular layer more nearly resembled the normal appearance than in any other part of the cerebellum, but even in these localities it was thin and consisted of underdeveloped cells intermingled with which were atrophic and misshapen Purkinje cells. Scarcely any cellular elements were distinguishable in the molecular zone of the cerebellum.

pyramis. All of the lobular and folial patterns of the vermis and lateral lobes were deficient and the fibre constituents were meagre. Nowhere was it possible to distinguish more than a few fibres ascending from the medullary core to the molecular layer. In consequence of this the longitudinal fibres in the molecular layer consisted merely of a few delicate threads. Anterior to the fissura prima transverse fissures were absent and there was practically no foliation.

Both middle peduncles were reduced in size, and on the right the staining was paler than on the left. The superior peduncles showed only a slight reduction in size as compared with the normal. The dorsal and ventral decussations of the superior peduncles, the thalamo-olivary tracts, the fasciculi longitudinales laterales, the mesial and lateral lemnisci, the mesencephalic fifth and the trochlear decussation compared favourably with similar structures in the normal animal.

FIG. 4.—Section through the metencephalon to show the rudimentary appearance of all of the constituents of the cerebellum, the lack of definition of the intracerebellar nuclei, and the deficiency of the juxtarestiform bundles.

Mesencephalon.—With myelin stains the superior and inferior colliculi with their brachia, the third and fourth nerves, the red nuclei and the fasciculi retroflexi did not show any appreciable variations from the normal animal. The optic nerves, chiasm and tracts appeared quite normal.

Diencephalon.—Technical difficulties precluded a detailed study of the basal ganglia at this time, and the results of this investigation will be published at a later time if the pathological morphology warrants it.

Telencephalon.—The centrum of the right hemisphere was almost entirely devoid of myelinized structures, but consisted of numerous corpora amylacea surrounded by a dense mass of cellular material among which fibrillar structures of glial nature could be distinguished. Capillaries were very abundant. The

of the extremities but merely bilateral co-ordination. In consequence of the demand for more perfect unilateral synergic control on the part of the bipedal mammals, and even in some of the lower mammalian quadripeds, the cerebellar hemispheres make their appearance. According to Bolk, the anterior and posterior crura of the lobulus ansiformis are present in all mammals, and contain unpaired centres for co-ordination of the muscles of each extremity. As we ascend from the lower to the higher mammals, and the independent movements of the limbs become more complex, the cerebellar hemispheres become more complicated in their lobular and folial patterns, thereby providing the neural centres and pathways that are necessary to provide for the unilateral synergic control of the individual movements of the extremities. This greater range of movement, therefore, is accompanied, *pari passu*, by the development of a greater cerebellar area.

In this case a part of both the neo- and palæo-structures was deficient as a result of arrested development. This arrest affected principally the right cerebral hemisphere, more especially the frontal and parietal areas with their pontile connections, but the same process involved, to a lesser degree, the medullary substance of the left cerebral hemisphere. The cerebellum, however, suffered the most and none of its constituents escaped. Every lobe, lobule, folium and foliette, together with their finer components, showed the results of the morbid process.

Summary.

The total myelinization in all the afferent and efferent cerebellar tracts was less than it should have been in an animal of this age. The main functional defect in this kitten was the inability to assume or maintain the optimum physiological posture, that is, the position of lying on its belly so that it could bring both legs under it. The animal could not get into this position, and in attempting to do so would roll over.

The animal was born without and never developed those tracts essential to the assumption and maintenance of the correct posture. Throughout life the chief symptoms were due to this very defect. This is the first component of behaviour to make its appearance in the newborn cat, and appears on an average of eight minutes after birth. At this period both the juxtarestiform bundles and the vestibulo-Deiterospinal tracts are well myelinized.

This animal showed but few signs of asynergia in the head and trunk movements, and none in the limb movements, but it must be remembered that all of these were of the most simple and primitive type.

Remarks.

The clinico-pathological features here presented are in agreement with the conceptions that the patterns for many of the unlearned reactions are phyletically conditioned, and that the formulæ for these patterns reside in the phylogenetically older regions of the brain and spinal cord. We know that at birth, or very soon after, all of the spinal and cranial nerve-roots of a cat are myelinized [1]. The tracts of the central nervous system that first receive their myelin sheaths are the fasciculus longitudinalis posterior, the fasciculus predorsalis, the vestibulo-Deitero-spinal complex, the cochlear tracts, the ascending mesencephalic and the descending spinal trigeminal bundles. Later the spino-cerebellar tracts with their connections to the vermis of the cerebellum, the cerebellar peduncles, the rubrospinal and the optic tracts receive their myelin. The behavioural studies made by Tilney and Casamajor [1] indicate that distinct correlation is possible between somatic behavioural components and myelinogenesis.

The earliest reaction pattern is concerned with posture and balance (vestibulo-Deitero-spinal). Tilney and Casamajor have enumerated the reactions of the domestic cat in the following order: (1) Postural; (2) crawling, approach; (3) sucking; (4) synergizing; (5) primitive escape; (6) eye opening; (7) eye and head turning; (8) sitting; (9) walking; (10) scratching; (11) avoiding; (12) running; (13) pawing; (14) washing; (15) auditional head and ear turning; (16) lapping; (17) escape; (18) climbing.

At least the first seven of these may be accounted for by the function of pathways consisting of cranial and spinal nerves which by way of the posterior longitudinal and predorsal fasciculi establish connections with the nuclei in the reticular formation of the mid-brain, bulb and medulla. An early contribution to synergized movement is supplied by the structures of the palæocerebellum, consisting of the nuclei of the vermis with their connections, the palæo-olive, the nucleus ruber, the substantia nigra, the thalamus and the palæostriatum. In the neocerebellum, represented by the lateral lobes, and the newer structures of the cerebrum, represented by the neostriatum and pallium, probably reside the pattern formulæ for the more complex and finely executed expressions of posture and movement, those late manifestations of somatic behavioural adaptation.

The simplest movement patterns require merely harmonious action of the axial musculature with co-ordination from segment to segment and bilateral synchrony. Such movements as swimming and the vermicular movements of reptilia and some amphibia require no independence

The cerebellum, although only slightly more than 50 per cent. of the normal size for the age, developed sufficient synergic capacity to give the animal adequate co-ordinative control in such movements as it did make. Because of its inability to assume the correct posture, it was unable to learn such acquired performances as washing its face with its paws, standing, walking, running, climbing, jumping, burying its fæces, hunting or other skilled acquired acts.

The agenetic defect of the right frontal and parietal areas, the bilateral lesions in the centrum ovale and the diminutive pyramid on one side, are other indications of the widespread morbid process in the brain that was operative in the prenatal period. That the animal showed no evidence of pyramidal disease as indicated by paralysis, lack of voluntary control, increased reflexes and tone, is due to the fact that the motor areas of the cortex are not essential for the early behavioural reactions in the kitten, and that a large range of movements, such as crawling, swimming and pawing, all with a more or less definite purpose, are possible through the activity of lower segments in the axis, probably the mid-brain. The absence of the pallio-ponto-cerebellar connections from the right hemisphere and the deficiency on the left side, is a histological condition which did not express itself in the symptomatology, because the animal had not advanced to that stage of motor organization in which neopallial-cerebellar co-operation is essential. This co-operation is necessary only to more highly skilled learned reactions.

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OBSERVATIONS CONCERNING PRIMITIVE REFLEXES AS REVEALED IN REACTIONS IN ABNORMAL MENTAL STATES.

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For the purpose of this presentation it is proposed to review certain observations of neurological interest made in connection with the study of behaviour disorders in abnormal mental states, in which were revealed striking similarities to reactions occurring in the embryo, in infancy and early childhood, especially with respect to the emphasis and dominance of primitive reflexes.

Attempts at purely psychological explanations of reactions in the psychoses seem to fail in some instances because many reactions appear non-mental in origin in a large measure, that is, they would appear to belong to lower biological levels.

The present study is concerned, therefore, only with symptoms which can be observed directly and examined without depending upon the patient's statements for any part of the explanation of the origin of the symptoms in question. We shall deal only with such phases of the adaptation of organisms to changing conditions of environment as are generally described under the term behaviour.

It is assumed that reflexes are primarily segmental responses, as contrasted with widespread reactions of the organism as a whole. The term primitive reflex is used to designate a mechanism by which a particular type of response is brought about by the activity of either a single nervous arc or several nervous arcs, such reflexes as have been observed in embryonic and later life in lower forms of animals and in human beings.

The second phase of the matter deals with functions that are inhibitory. Neural excitations of sufficient duration and intensity to dominate the activity of the organism for the moment, and capable of neutralizing or counteracting the effect of an excitation which normally would bring about the response in question, are regarded as inhibitory.

Influences, both internal and external to the nervous system and the soma, are arising constantly tending to modify the activity of reflexes.

An organism cannot respond to two stimuli at the same instant, if the stimuli are at all antagonistic. The effect of a stronger stimulus may outweigh and inhibit response to a weaker stimulus, so that the response which otherwise would have occurred is nullified. The most obvious example is presented in the acts of flexion and extension.

Although inhibition is one of the most important potentialities of the nervous mechanism, it is one about which little is known, especially if one regards inhibition as a specific function of nervous structure. If, however, inhibition be considered as an effect brought about by neuronic activity, the matter becomes less obscure. In order to inhibit a particular act, some other mode of activity must be initiated. Co-ordination of action would appear to be the result of the effects of inhibitory activity as much as an effect of direct stimulation and response. If one form of response is considered as dominant at one moment, and another at another moment, we have a key to the study of the functional effects of inhibition upon the organism.

Inhibitory processes as such can be studied only by their effects. In the embryo this cannot be done accurately. Minkowski, nevertheless, observed what appeared to be an inhibitory effect upon certain movements of the extremities in a 19-cm. fœtus, the excitation of one extremity to a state of flexion being at first followed by extension of the opposite extremity (leg), but continued stimulation later appeared to produce extension of the same extremity [2].

In the adult, the chain of events involved in inhibitory processes becomes more and more complex as experiences multiply through training and habit. It would seem, therefore, that inhibitions in their simplest forms, as in childhood primarily, are largely sensory. Stimuli of smell, taste and touch, which initiate the sucking and swallowing reflexes, are strongly inhibitory against other stimuli, with the probable exception of painful stimuli, as is shown by the soothing effect of feeding upon the restless infant.

Inhibition may serve as a defence reaction, as in the avoidance of movements in the direction of danger; that is to say, some antagonism is set up against certain response dispositions.

In general, it may be said that inhibitory processes may be accounted for as follows:—

(1) The antagonism of the action because of anatomical arrangement of muscle groups, e.g., flexion and extension.

(2) Differences in intensity of action of environmental energies.

(3) Internal stimuli (including emotional stimuli) which determine the attitude assumed by the organism towards the source of stimuli.

(4) The effect of ideas (education, experience).

The higher the position in the phylogenetic scale and the greater the advancement in the development of the individual, the more potent becomes the functional value of inhibition to the organism. Inhibitory influences may be localized or diffuse in their effects, involving a single set of opposing muscle groups, as in flexion or extension; or the influence may appear as a widespread response, such as the shudder reflex, or as a generalized muscular rigidity such as produces the well-known immobility commonly observed during states of fright.

According to the "postural tension" theory (Bechterew), responses may arise from the several "urges," namely, hunger, fear, anger, shame, disgust, grief and love, which originate in sensory experiences and their corresponding emotional states, arising simultaneously with the stream of impulses from the viscera, and in their turn may affect the entire organism and guide its activities through the non-striated and striated muscular mechanisms.

In normal states, primitive reflexes may operate as pure reflexes; they may be initiated as pure reflexes and terminate as instinctive acts or emotional responses (the line of separation between these cannot be sharply drawn); they may become more or less completely under control through direction or choice of action and, therefore, may terminate as volitional acts.

Complex acts terminating as adaptive responses without previous training or representation in consciousness are assumed to constitute instinctive acts. From this point of view, therefore, some reflex acts may be regarded as instinctive acts. All instinctive acts are assumed to be constituted of primitive reflexes.

For elucidating the theme under consideration, a few of the observations made upon human embryo may be cited from the literature, especially those of Minkowski.

The contributions of Preyer (1885), Feldman (1920), and Minkowski (1921) contain the reports of their own observations, in addition to those of other investigators, concerning the physiology of embryos of invertebrates and vertebrates, including the human nervous system.

Movements of the head of a four-months' fœtus kept alive in physiological saline solution were observed to continue for one half hour. Also, slight movements of the extremities were seen in a 24-cm. ($4\frac{1}{2}$ months') embryo. The patellar and Achilles reflexes were not obtained, but percussion of the muscles produced contractions resulting in abduction of the limb and plantar flexion without action of the great toe (Krabbé, 1912). Bersot (1920) saw movements of opening the mouth and a "modified Babinski" in a fœtus 4 to 5 months' old; also flexion of the toes and drawing back of the lower limb in a fœtus of

28 weeks. At 35 weeks there were rigidity of the extremities and reactions resembling athetoid movements. The presence of hairs and vernix caseosa in the meconium suggest that sucking movements occur in the fœtus.

Minkowski's researches upon the human fœtus were conducted at the time of Cæsarian sections done under local anæsthesia, the fœtus being observed while immersed in physiological salt solution. Movements of the head, trunk and extremities (about a single articulation) and isolated movements of the fingers and thumb were studied. Choreio-athetoid movements, especially choreiform, were observed more frequently as the age advanced in the examples studied.

In a 23-cm. fœtus, movements resembling respiratory acts, consisting in "extension" of the thorax with retraction of the head, were observed. Opening and closing of the mouth, with movements of the arms, were seen in 13·5 and 20-cm. fœtuses.

Cutaneous reflexes appeared less isolated, that is, there was a strong tendency for the response to radiate to the opposite side even when resulting from slight stimuli. The Babinski response was observed in a 21·5-cm. fœtus, accompanied by movements of the head and trunk. At 3 to 5 months the responses became more constant with less tendency to radiation. In a 4-months' fœtus (16 cm.) spontaneous dorsal flexion of the great toe was noted. Touch stimuli applied at the internal canthus of the eye produced contractile movements of the lid in a 21·5-cm. fœtus, that is, before the palpebral fissure appeared.

Mucous reflexes, shown as elevation of the chin following stimulation of the surface of the lip, were seen in an 11-cm. fœtus; in the 21·5-cm. fœtus (4 months plus), touching the tongue with a sound caused the mouth to open and close, and elevation of the chin as in the swallowing reflex. When the head was turned, the arm of the side towards which the head was turned moved ("tonique réflexe").

In no case did mechanical excitation of the cerebral hemispheres produce any response, but stimulation of the bulb (medulla) with a sound produced movements of the mouth in a 4-months' fœtus.

Illustrative applications.—In patients with organic cerebral degenerative processes accompanied by advanced dementia, the case for the primitive reflexes seems self-evident. In the advanced arteriosclerotic dementias, volitional responses may be entirely absent, yet local paralysis may not be demonstrable. The same may be true in cases of terminal general paralysis (paresis).

If motor impulses are not interrupted, that is, if palsy be not present in the neural arcs concerned, we almost invariably found the *swallowing* and *sucking reflexes* preserved. It was also possible to initiate these

reflexes by the application of touch stimuli to the periphery of the fifth, seventh or ninth cranial nerves, as when an object was brought in contact with the skin or mucous membrane, especially of the region of the lips or the orbicularis oris. In some instances visual stimuli were sufficient to evoke responses, as when a spoon or feeding cup was brought within the visual field; not infrequently there was pouting of the lips together with apprehensive movements of the entire head. In this connection it may be mentioned that the pouting reaction has been observed in patients *in extremis* when touch stimuli were applied to the lips.

In a similar manner, the *grasping reflex*, which according to Watson is so strong in infancy that a child can support the weight of its body as late as the 120th day or longer, was seen to have returned in all cases of organic dementia examined. For example, in attempting to move the patient in bed, the stimuli usually were seen to evoke the grasping reflex, the hand clutching whatever object might be near; sometimes the grasping reflex was made active in both hands. The reflex frequently became so strongly active that attempts to release passively the patient's hold served only to stimulate the muscles to a tighter grasp. The most effective mode of interrupting the reflex thus evoked was to initiate some other reflex to the point of dominance, thus inhibiting the grasping reflex.

The primitive dominance of *flexor reflex responses* is striking in states of mental depression. In states of mental depression we have to face the controverted question of the priority of the emotional state or the visceral component of the reaction, that is, whether in accordance with the James-Lange theory the visceral reaction *is* the emotion.

According to the postural tension doctrine cited above, the emotional stream from the viscera is carried by the autonomic nerves to the roots which supply the skeletal muscles, just as the hunger urge arising from the muscle tonus in the wall of the stomach is carried to the neurons supplying the skeletal musculature. In one case reactions may be produced which correspond with states of fear or anger; in the other, reactions concerned in the seeking of food.

Accepting the primitive reflex concept to explain the somatic responses in profound depressions, the total absorption of the patient's attention (consciously or unconsciously) by persistent emotional states (usually painful in depressions), excludes the influence of inhibitory excitants and thus allows the dominance of primitive reflexes. Such responses are commonly observed in the form of the shrinking and crouching attitudes as are seen in fear reactions. In some instances, the dominance of flexion over extension became so pronounced as to

make the patient assume the fœtal position. Macpherson (1913) has discussed similar observations in connection with "Instinctive Reactions in Mental Disorders," applying McDougall's treatment of the subject of instincts.

In states of mental excitement or exaltation, as in attitudes of normal aggression, of anger, disdain, or of superiority, the dominance of extensor response appears.

In the schizophrenic types of reaction there appears an array of primitive reflex behaviouristic responses. The behaviour of the dementia præcox patient is conspicuous on account of its incongruity. Many of the reactions are distinctly of the reflex and automatic type. Impulsive reactions to apparently unimportant stimuli are frequently noted in the clinical data as responses which occur "without provocation." The destructiveness, aggressiveness, and the hoarding propensity are illustrations of the well-known primitive reflexes usually termed instinctive acts. The hand to mouth reflex universally present in infancy and in low-grade imbecility is conspicuous in many schizophrenics.

In general, it may be stated that the reflexes appearing earliest in the order of functional development are apt to be the last to disappear in the process of functional disintegration. In a similar manner the last to be acquired are likely to disappear early in the course of the dementia.

When inhibitory influences are removed as the result of functional disintegration, primitive reflexes control the types of response to such an extent as to make them stand out conspicuously.

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DISCUSSION.

Dr. Adolf Meyer said the presentation of the matter reinforced the sense of unity of man, and further illustrates what had long been pointed out by Oppenheim, who described the reappearance of the sucking reflex in cases of cereberal reduction and states close to coma. Minkowski's systematic observations on the surviving human fœtus have furnished a great deal of material towards rounding off a picture of man as a living natural history object, a consistent entity, a product of biological, structural and functional integrations, including the simplest neural functions as well as the most elaborate reactions which are treated as psychology or functions of personality.

A CASE OF CORTICAL DEAFNESS.

BY EDWIN BRAMWELL, M.D.EDIN.

DR. EDWIN BRAMWELL described the leading clinical features and showed the brain of a patient who had become completely deaf as the result of softenings in both temporal lobes.

The history of the case was briefly as follows: A right-handed woman of 62, the subject of mitral stenosis, suddenly developed, upon June 12, 1927, a sensory aphasia and paraphasia. Twelve days later she presented symptoms of another cerebral attack. Upon admission to hospital the patient was found to be completely deaf. Examination of the ears showed no abnormality of the membranes. According to the patient's sister her hearing had been quite acute prior to her illness, and Dr. A. Y. Cockrane, who saw the patient on several occasions between her first and second attacks, was satisfied that she was not deaf during this period. The diagnosis of embolic softenings in both temporal lobes was suggested. Upon July 10 the patient died of pneumonia.

The *post-mortem examination* showed an extensive softening in the left hemisphere, involving a large part of the two upper temporal convolutions, and on the right side a more localized softening involving the supramarginal gyrus as well as the upper and posterior part of the left superior temporal convolution.

Similar cases have been reported by Friedländer and Wernicke, Pick, Mills, Anton, Sérieux and Mignot, and Mott.

This case will be recorded in detail in *Brain* when the examination of the brain has been completed.

DISCUSSION.

DR. ADOLF MEYER said that Pierre Marie claimed from the strictly clinical point of view that we have no adequate knowledge of the relation of the temporal lobe to hearing, and of the relation of hearing to aphasia. It is, therefore, important to learn of a case, as that presented, although in this patient there was no opportunity for an adequate adjustment and recovery from the immediate reaction of the brain to the lesion, as an examinatiou was possible during that period only when the acute disturbances might account for the extensive loss of hearing. A complete anatomical examination, especially of Heschl's convolutions, and the exact determination of the extent of the

lesion from the island of Reil out towards the surface would be necessary to give the case its full value.

Examination of a series of cases of auditory aphasia has shown that the point of the auditory cortex involved by the lesion is important. He found from his own cases and those collected from the literature that, with very few exceptions, permanent word deafness occurred only when the brain between the island and Heschl's convolution was destroyed, and thereby the whole afflux of the auditory fibres to the left auditory centre was cut off. Bilateral vascular lesions in the temporal lobes have usually produced symptoms of word deafness only; so-called pure word deafness without paraphasia has hitherto usually been attributed to bilateral lesions, in which, however, deafness is not present. In the present case there was evidently general deafness, but it may have been only a temporary symptom that might in part have cleared up if the patient had lived longer.

COMPARATIVE CHEMICAL STUDIES OF THE BLOOD AND SPINAL FLUID IN EPILEPSY.

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NUMEROUS arguments have been proposed, attempting to ascribe a chemical or metabolic basis to the convulsions of idiopathic epilepsy. Despite a vast amount of work in this field, it has not been possible to demonstrate any organic cause for the convulsions, though the progressive course of the disease is not unlike that of familiar metabolic disorders. The fact that starvation or a restriction of some foodstuffs in the diet, and a diminution of mental or emotional strain, are followed by a partial relief of symptoms, lends additional support to the belief that the convulsions may have a metabolic ætiology. Further, the convulsions of tetany, spasmophilia, nephritis and eclampsia can be explained by metabolic abnormalities, and can be relieved by chemiotherapy. But a critical examination of these arguments as stated in the literature reveals, that although much clinical evidence suggests a metabolic origin of the convulsions of idiopathic epilepsy, there is a conspicuous lack of biochemical data in support of it.

This report presents a part of the results obtained in a comprehensive study of the chemical composition of the blood and spinal fluid in epilepsy. The object of this investigation was to determine whether these body fluids presented evidence of any characteristic qualitative or quantitative change in composition, either during the interval period or in relation to the epileptic seizure. During the course of this study, 130 cases of idiopathic epilepsy have been observed, representing both sexes and varying in age from 3½ to 69 years. Of these subjects, 100 were psychotic inmates of the Manhattan State Hospital for the Insane, New York City; their ages ranged from 22 to 69 years, and included sixty-four females and thirty-six males. All of the patients in this group were maintained

throughout their entire stay in the institution upon a standard diet, composed of 40 grm. of protein, 50 grm. of carbohydrate, and 50 grm. of fat, and yielding 2,500 calories per day. We are indebted to Dr. C. Floyd Haviland, superintendent of the institution, for the privilege of studying these patients, and to Dr. John Notkin for his assistance in the selection of the cases, and in the collection of specimens for analysis. Thirty of the subjects reported here were in the neurological service of the New York Post-Graduate Hospital, and their ages varied from 3½ to 33 years. Roentgenograms of the heads of the patients in this group revealed no abnormalities, and Erb's electrical reactions were employed to exclude instances of spasmophilia.

All patients were selected for study only after a complete physical and neurological examination had disclosed no objective evidence of disease of the central nervous system. A chemical examination of the blood, as well as clinical examinations, were used to exclude cases of tetany. All of the patients reported had negative blood and spinal fluid Wassermann reactions, and the colloidal gold curves, butyric acid test and cell counts of the cerebro-spinal fluid showed no variation from the normal. Specimens of blood and spinal fluid were drawn for analysis after a night's fast during the interval period, and again, when possible, immediately after a seizure. Both fluids were obtained as nearly as possible at the same time ; first, the blood was drawn from a vein in the arm, and then the spinal fluid by lumbar puncture. Prompt analyses of the specimens obviated any changes due to glycolysis or autolysis. Results of the analyses of these fluids are presented in the following tables and charts. Apart from their possible bearing upon the ætiology of epileptic convulsions, these studies have enabled us to assemble valuable data on the relative distribution of various compounds between the blood and cerebro-spinal fluid.

Lennox and Wright [1] have given comprehensive data for the non-protein nitrogenous compounds of the blood of epileptic patients. In a large group of epileptics, examination of the blood for total non-protein nitrogen, urea nitrogen, amino-acid nitrogen, uric acid and creatinine showed these constituents to be within normal limits. As our experience agrees with the findings of Lennox and Wright, we are not reporting the data for the non-protein nitrogenous components of the blood. Lennox and Wright conclude from their observations that epilepsy is not accompanied by an impairment of kidney function as it concerns the excretion of the nitrogenous waste products. Moreover, there is no change in protein metabolism of such magnitude as to effect the concentration of the enumerated protein catabolites in the blood.

An analogy between tetany and the epileptic seizure has been sug-

gested by Bigwood [2]. He attributes the onset of the convulsion to a deficiency in blood-calcium as a consequence of an alkalosis. Rosello [3] advocates calcium therapy for the relief of epileptic seizures, but the animal experiments upon which Rosello bases his therapy are far from conclusive. Convulsions were produced in animals by the intraperitoneal administration of sodium citrate, and these convulsions were relieved by calcium chloride introduced into the peritoneal cavity or into a vein. The frequency of epileptic seizures during the menstrual period were ascribed to a loss of calcium at this time. Moreover, Rosello believes that the efficacy of sodium bromide therapy in epilepsy is not due, as is generally believed, to a replacement of chlorine by bromine, but rather to a decrease of the ratio $\frac{\text{NA ion}}{\text{CA ion}}$ of the blood. The relation of the increased irritability of the neuro-muscular mechanism to a decrease in blood-serum calcium has frequently been demonstrated. Howland and Marriot [4] found low values for the calcium of the blood-serum of children with infantile tetany, and subsequent observers confirmed these observations. Greenwald [5] states, "There can be no doubt but that the tetany of parathyroidectomized dogs is due to a disturbance in calcium and phosphorus metabolism." Moreover, the convulsions seen in the acidosis of chronic nephritis with phosphate retention can be attributed to a reduction of blood-serum calcium (Marriot and Howland [6], Halverson, Mohler and Bergeim [7], Feigel [8], Denis and Hobson [9], Salvesen and Linder [10], Schmitz, Rohdenburg and Myers [11]).

TABLE I.—CALCIUM OF BLOOD AND SPINAL FLUID IN EPILEPSY.

	Patient	Blood Ca.	Sp. Fl. Ca.	Previous seizure, days	Ratio Sp. Fl. Ca to Bld. Ca.
1.	G. P.	11·5	6·0	3	0·52
2.	C. G.	12·1	6·2	6 hours	0·51
3.	A. H.	11·1	6·3	At time of seizure	0·56
4.	M. R.	11·1	5·9	At time of seizure	0·53
5.	R. McK.	10·0	5·6	3	0·56
6.	G. P.	10·6	5·6	2	0·52
7.	A. S.	10·6	5·0	1	0·47
8.	K. K.	10·4	5·8	1	0·55
9.	A. S.	10·6	6·0	1	0·56
10.	H. H.	12·8	5·9	1	0·46
11.	F. L.	10·8	5·2	1	0·48
12.	A. W.	10·7	5·4	15	0·54
13.	A. M.	10·7	5·4	10	0·54
14.	M. W.	9·5	5·0	8 hours	0·52
15.	M. M.	10·5	5·5	—	0·52
16.	M. L.	11·1	5·7	—	0·51
17.	J. O'B.	11·3	6·1	—	0·54
18.	S. B.	11·4	5·5	—	0·48
19.	W. B.	11·2	6·1	1 hour	0·54
	Average	10·94	5·68	—	0·51

In order to determine whether there was any demonstrable relation between the epileptic seizure and blood or spinal fluid *calcium* content,

calcium estimations have been made in these two body fluids during the interval period and at the time of seizure in nineteen cases of epilepsy. The method of analysis employed was that described by Clark and Collip [12]. The normal range of blood-serum calcium lies between 9·6 and 12 mg. per 100 c.c., and the values for the blood-serum calcium of the nineteen epileptics are within these limits, with but one exception, (Case 2, C.G., Table I), who gave 12·1 mg. per 100 c.c. The average for the series is 10·94 mg., showing no significant variation from average of 10·1 mg. for seven normal adults reported by Salvesen and Linder. In spinal fluid less calcium is found, varying from 5·2 to 6·1 mg. per 100 c.c., giving an average of 5·68 mg. per 100 c.c. There is evident a fairly constant ratio of spinal fluid to blood-serum calcium, the average being 0·51 with extremes of 0·48 and 0·56.

When this study of the calcium of the blood-serum and spinal fluid had been partially completed, Hamilton [13] published data on a comparison of the concentrations of some inorganic substances in serum and spinal fluid. For sixteen cases of epilepsy he has found a mean for blood-serum calcium of 10·8 mg., and for the spinal fluid 5·6 mg. per 100 c.c., the ratio of spinal fluid to blood-serum calcium would be 0·51. Hamilton's results are in close agreement with those presented in Table I.

Within recent years numerous investigations have been made on the state of the inorganic components of the blood-plasma or serum, and their ability to pass into other body fluids by diffusion. Neuhausen and Pincus [14], by analysis of pig sera, their ultrafiltrates and residues, have shown that the chlorides, phosphates, sodium and potassium are totally diffusible, but from 30 to 50 per cent. of the calcium is in a non-diffusible form. Rona and Takahashi [15] found 75 per cent. of the calcium of pig sera diffusible; Cushny [16], 62 to 70 per cent. of oxen sera calcium; Moritz [17], 62 per cent. of calcium of rabbit sera; Updegraff, Greenberg and Clark [18], 39 to 65 per cent. of the total calcium of human and animal blood; von Meysenbug, Pappenheimer, Zucker and Murray [19], 60 to 70 per cent. in normal men and dogs; and in rickets and in experimental tetany von Meysenbug and McCann [20] found the diffusible calcium is from 60 to 70 per cent. of the total. Most observers agree that the non-diffusible blood-serum calcium is bound to the serum proteins or some component of the serum proteins. Cameron and Moorhouse [21], however, state that in dog's plasma part of the total calcium exists in inorganic combination (53 per cent.) and a part in specific organic combination (47 per cent.). The nature of the organic radicle with which the calcium is combined is not known. This calcium in organic combination dissociates only slowly when the calcium ions

are removed. Observations made by Greenwald suggest that the calcium content of the plasma is normally maintained at a constant level by an equilibrium between inorganic calcium and an organic compound of calcium.

Resemblance between this organic compound of calcium and calcium citrate is indicated, but the substances are not identical. Greenwald further believes that the parathyroid hormone is necessary for the formation of this organic constituent. The diffusible calcium of the blood-serum (or plasma) is not wholly in an ionic form. Holt, La Mer and Chown [22] conclude that the amount of ionized calcium in blood-serum cannot be more than 2·5 mg. per 100 c.c. Neuhausen and Marshall [23] have compared the ionic concentrations of sodium, chlorine and calcium, determined electrometrically, with the total concentrations of these elements in the blood-serum determined by the ordinary analytical methods. They find that the sodium and chlorine are present as in aqueous solution of sodium chloride of the same concentration, but only about 10 per cent. of the total calcium is in ionic form. In the electrodialysis of blood-serum, Bernhard and Beaver [24] noted that not more than 28 per cent. of the total calcium was dialysable, and this probably represents the concentration of calcium ions.

The calcium content of the cerebro-spinal fluid appears to be definitely less than the diffusible calcium, but greater than the calcium ion concentration of the blood-serum. So far as we know, the calcium ion concentration of cerebro-spinal fluid has not been determined. Marrack and Thacker [25] conclude that the distribution of calcium in body fluids, including cerebro-spinal fluid, is such as would occur if they contained on an average of about 5·5 mg. of calcium per 100 c.c. as ion, and in addition undissociated calcium proportional to the protein concentration. In fifteen normal dogs, Cameron and Moorhouse observed that the calcium of the cerebro-spinal fluid was 53 per cent. of that of the blood-serum, but in tetany, following parathyroidectomy, the figures for serum calcium and cerebro-spinal fluid calcium tended to become exactly equal. In three normal individuals, Pincus and Kramer [26] report a mean concentration of calcium in spinal fluid as 43 per cent. of that of blood-serum. The calcium of the spinal fluid in one instance of epilepsy in a child was 51 per cent. of the blood-serum calcium, and in one case of acute nephritis with some phosphorus retention the calcium of the cerebro-spinal fluid was 61 per cent. of the blood-serum calcium. This high ratio was due to the fact that the blood-serum calcium was reduced. Halverson and Bergeim [27] have studied the calcium content of the cerebro-spinal fluid in tabes dorsalis and miscellaneous pathological conditions of the central nervous system They report figures varying

from 4·8 to 6·0 mg. per 100 c.c. The figures presented in Table I for the calcium of the blood-serum and spinal fluid of epileptics are in agreement with similar data for normal dogs (Cameron and Moorhouse), normal individuals (Pincus and Kramer), and for organic neurological conditions (Halverson and Bergeim). Comparing the findings in epileptics with results obtained in tetany (Moorhouse and Kramer), and in nephritis (Pincus and Kramer), it is evident that no analogy exists between the ætiology of convulsions in tetany or nephritis and those of epilepsy, so far as the calcium metabolism is concerned. Moreover, at the time of the seizure there is no variation demonstrable in the content of calcium in the blood or spinal fluid from that noted during the interval period. It is logical to conclude, therefore, that the onset of the epileptic seizures is not due to a reduction of the total calcium content of either the blood-serum or cerebro-spinal fluid. In this respect our observations do not corroborate those of Reiter [28], who has reported a level of the blood-calcium slightly below the normal, and in one individual he obtained figures as low as 7·1 mg. per 100 c.c. Moreover, the marked variations noted by Reiter for the blood-calcium of the same individual on repeated analyses are contrary to all recorded facts concerning calcium metabolism. The probability of a change in calcium-ion concentration will be discussed later.

TABLE II.—INORGANIC PHOSPHORUS OF BLOOD-SERUM AND SPINAL FLUID IN EPILEPSY.

Patient	Age	Sex	Blood-serum Inorganic P.	Spinal fluid Inorganic P.	Spinal fluid P. / Blood P.
1. M. C.	40	F.	4·5	1·9	0·42
2. H. G.	54	F.	3·6	1·8	0·50
3. L. P.	53	F.	3·8	1·4	0·37
4. J. N.	39	F.	2·7	1·3	0·48
5. E. R.	22	F.	3·7	1·6	0·43
6. H. G.	68	F.	3·4	1·7	0·50
7. A. A.	62	F.	2·5	1·2	0·48
8. M. L.	56	F.	3·8	1·7	0·42
9. M. L.	52	F.	3·6	1·4	0·38
10. E. McG.	—	F.	4·2	1·7	0·40
11. E. B.	—	F.	3·9	1·8	0·46
		Average	3·51	1·59	0·45

The relative concentrations of *inorganic phosphorus* in the blood-serum and spinal fluid have been studied in eleven cases of epilepsy. Determinations of inorganic phosphorus were made by the method of Benedict and Theis [29]. Salvesen and Linder give as the range for the inorganic phosphorus of the blood-serum of normal adults, from 3·4 to 4·6 mg. per 100 c.c., with an average of 3·8 mg. per 100 c.c. In the series of eleven adults with epilepsy, reported in Table II, the inorganic phosphorus varied from 2·5 to 4·5 mg., establishing an average of 3·51 mg. per 100 c.c. This average is slightly below that of Salvesen and Linder,

but this deviation may be due to differences in age of the individuals examined. Moorhead, Schmitz, Cutter and Myers [30] have reported figures for the inorganic phosphorus of the blood for normal individuals of different ages. From their data it is seen that the inorganic phosphorus of the blood diminishes with advancing age. Their average of 3·6 for the period of life represented by the cases in Table II corresponds well with our average figures of 3·51. The inorganic phosphorus of the spinal fluid forms from 37 to 50 per cent. of that of the blood-serum. The average inorganic phosphorus of the spinal fluid is 1·59 mg. per 100 c.c., forming 45 per cent. of the inorganic phosphorus of the blood-serum. Although the figures for the inorganic phosphorus of both blood and spinal fluid show relatively large variations from the mean figures, amounting to about 33 per cent., the figures for the ratios of spinal fluid to blood inorganic phosphorus are surprisingly constant. It is evident, then, that in the epileptics examined the inorganic phosphorus of the spinal fluid varies directly with the concentrations of this element in blood-serum or plasma. In the data reported by Pincus and Kramer for the concentration of inorganic constituents of the blood-serum and spinal fluid of normal individuals, the average figure for the inorganic phosphorus of the spinal fluid forms 42 per cent. of the mean value for the inorganic phosphorus of the blood-serum. However, the increase in the inorganic phosphorus of the blood-serum in pathological states is not reflected in similar increases in the spinal fluid. Cohen [31] has found an average of 3·28 mg. of inorganic phosphorus for the blood-plasma, and 1·58 mg. for the inorganic phosphorus of the spinal fluid in six normal individuals, the average for the spinal fluid forming 48 per cent. of that of the blood-plasma. Cohen also noted increases in inorganic phosphorus of the blood-plasma in pathological conditions without similar increases in the spinal fluid. The results reported in Table II for the relative concentrations of inorganic phosphorus in the blood-serum (or plasma) and in the spinal fluid in epilepsy correspond with those reported for normal individuals. There is a close relationship between calcium and phosphorus metabolism in the body, both in health and in disease, and it is significant, we believe, that the finding for the inorganic phosphorus of the blood-serum and spinal fluid in epilepsy are analogous to those reported for calcium.

Pighini [32] has reported a study of the *cholesterol* of the spinal fluid in some mental diseases. In four normal individuals no cholesterol was found, but in twenty-two cases of epilepsy crystals in the fluid were identified as cholesterol, and the number of crystals were reported to be proportional to the gravity of the disease. Pezzali [33] observed a uniform decrease in blood-cholesterol during the epileptic seizure, with a

subsequent rise. The regular fluctuations of the cholesterol content of the blood, according to Pezzali, indicate that this may have a protecting action, and hence advocates cholesterol therapy. Popea and Vicol [34] confirm these observations of Pezzali. They also have reported in sixteen epileptics a drop in blood-cholesterol during the epileptic convulsions, and, since their patients had frequent seizures, the blood-cholesterol remained low during the interval period. Brain [35] has compared the level of the blood-cholesterol in a large group of epileptics with concentration of blood-cholesterol in a group of normals. The blood was obtained from the epileptics without special relation to the fit. The average figure for 102 epileptics was 165 mg. of cholesterol per 100 c.c. of whole blood, and for 71 normals the mean value was 173 mg. per 100 c.c. For the epileptics the average figure is 8 mg. per 100 c.c. less than the average figure for the normals, a decrease amounting to 4 per cent. of the average normal figure. However, when the blood was drawn from the epileptics within twenty-four hours after the seizure, the epileptics' blood gave figures for cholesterol 15 per cent. less than tho normal average. Repeated determinations of cholesterol in the blood of two epileptics showed that the attack was preceded by a prolonged fall in the level of the blood-cholesterol.

TABLE III.—CHOLESTEROL OF BLOOD AND SPINAL FLUID IN EPILEPSY.

Case	Patient	Age	Sex	Time since previous seizure	Cholesterol mg. per 100 c.c.	
					Blood	Spinal fluid
1	M. M.	42	F.	0 days	128	0
2	M. L.	56	F.	12 hours	144	++
3	J. O.	48	F.	42 days	125	0
4	S. B.	51	F.	70 days	150	++
5	D. S.	26	F.	7 days	137	0
6	F. W.	47	F.	3 days	127	0
7	M. C.	40	F.	2 days	093	approx. 10 mg. per 100 c.c.
8	H. G.	54	F.	0 days	171	0
9	J. C.	18	M.	1 day	171	++
10	A. G.	35	M.	—	143	0
11	P. O'C.	58	M.	—	122	++
12	J. A.	26	M.	6 days	164	0
13	F. B.	—	M.	8 days	125	++
14	A. J.	27	M.	—	173	+
15	T. B.	36	M.	—	157	0
16	W. K.	22	M.	1 day	131	0
17	A. J.	56	M.	2 days	130	+
18	A. H.	47	M.	20 days	165	+
19	H. P.	31	M.	16 days	137	0
20	M. J.	17	M.	2 days	141	++
21	N. K.	34	M.	25 days	148	+
22	W. J.	20	M.	10 hours	111	0

In twenty-two cases of epilepsy the cholesterol of the blood and spinal fluid has been determined by the method of Myers and Wardell

[36]. The authors of the method find the normal value of cholesterol of whole blood to vary from 140 to 160 mg. per c.c. Of the cases reported in Table III the values for the cholesterol of the blood vary from 93 to 171 mg. per 100 c.c.; eleven of these patients having values within or slightly above the normal limits. Since it is well known that the blood-cholesterol is decreased in both primary and secondary anæmias [37], it is probable that the low figures may be due to a coincident anæmia. In those instances in which the cholesterol has been determined less than twenty-four hours after a seizure (Cases 1, 2, 8, 22) no uniform change in the cholesterol content of the blood was observed. Of these four individuals, one has a normal, one an increased, and two moderately decreased concentrations. In all instances the blood was drawn in the morning before breakfast.

Somach and Halpern [38] in this laboratory have studied the variations in the cholesterol of whole blood of normal individuals drawn at intervals of two hours throughout a period of twenty-four hours. The data obtained for four individuals are presented graphically in Chart I. The figures upon which the graphs are based were checked by duplicate determinations. Throughout the day the variations in the cholesterol concentration of the blood may range from 10 per cent. above to 20 per cent. below the mean value, but the figures obtained for the specimens of blood drawn before breakfast are closest to the average of all determinations for the day. The deviations from the mean of the various figures for the cholesterol at different periods during the day are greater than the differences noted by Brain between the cholesterol concentration of normal blood and its concentration in the blood of epileptics. Since Pezzali, Popea and Vicol, and Brain have not considered in their studies the possible influence of associated pathological conditions, e.g., fever or anæmia, upon the blood-cholesterol, or the variations in cholesterol concentration at different periods during the day, it is questionable whether their observation of a diminution of the cholesterol of the blood in epilepsy has any significant bearing upon the problem of the ætiology of the epileptic seizure.

Before the extraction of cholesterol, the spinal fluid was concentrated five to ten times by carefully evaporating 5 or 10 c.c. upon a water bath to one-tenth of its original volume. Anhydrous calcium sulphate was then added to the concentrated fluid and the procedure followed as for blood. In one instance the cholesterol of the spinal fluid could be approximated as about 10 mg. per 100 c.c. In nine specimens a colour reaction was obtained, but the amount of cholesterol present was far too small for a quantitative determination, hence the cholesterol is reported as traces. No colour reaction was noted in six cases. If cholesterol

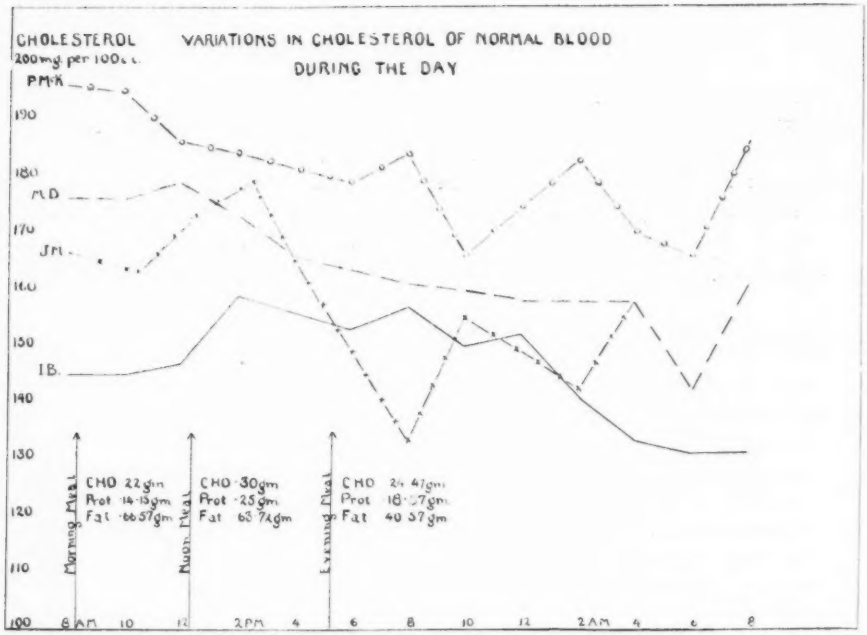

CHART 1.

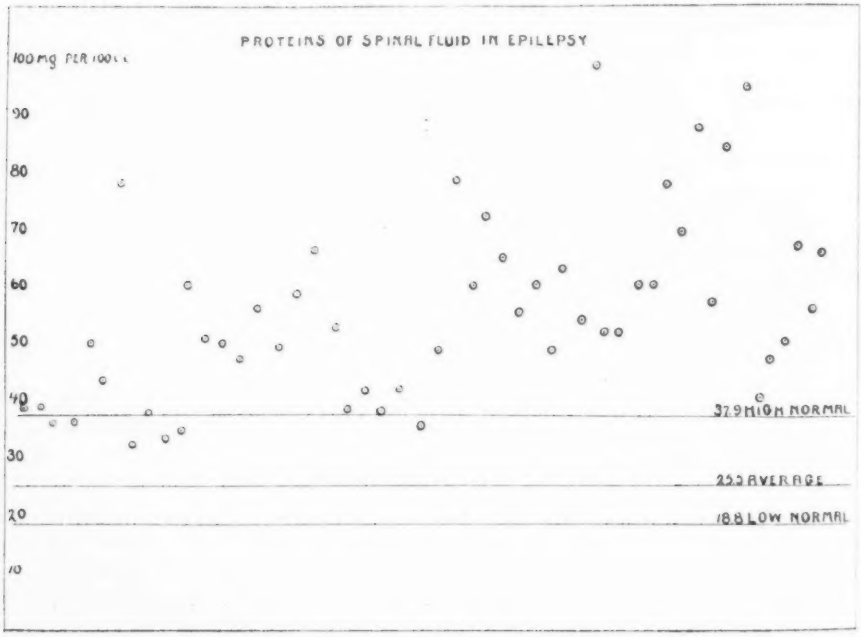

CHART 2.

occurs in the spinal fluid of epileptics, the amount present is minute. Our results do not confirm the contention of Pighini that cholesterol can be identified microscopically in the spinal fluids of epileptics.

TABLE IV.—PROTEIN CONTENT OF SPINAL FLUID IN EPILEPSY.

No.	Patient (female)	Protein mg. per 100 c.c.	No.	Patient (male and female)	Protein mg. per 100 c.c.
1	M. W.	39·2	34	G. P.	60·3
2	M. B.	39·5	35	A. S.	60·3
3	M. R.	36·2	36	K. K.	78·5
4	J. M.	36·9	37	A. S.	69·8
5	M. L.	50·5	38	J. D.	88·8
6	T. H.	44·0	39	P. O'C.	57·3
7	H. H.	32·9	40	F. B.	84·9
8	E. J.	38·2	41	J. M.	95·5
9	A. T.	33·9	42	C. L.	40·9
10	C. G.	34·9	43	F. B.	47·7
11	A. K.	50·2	44	G. M.	50·4
12	M. D.	47·7	45	J. C.	67·4
13	I. S.	56·7	46	H. M.	56·1
14	K. K.	59·0	47	W. H.	66·2
15	L. V. O.	49·8	48	A. H.	79·0
16	A. J.	39·0	49	J. E.	60·6
17	K. C.	42·1			
18	S. C.	38 2			
19	R. R.	42·1			
20	M. M.	38·2			
21	L. V. O.	49·4			
22	E. R.	79·6			
23	K. C.	60·3			
24	A. A.	72·9			
25	H. G.	65·1			
26	A. S.	55·9			
27	S. D.	60·3			
28	I. H.	49·4			
29	G. P.	63·7			
30	J. N.	54·5			
31	L. S.	99·6			
32	M. T.	52·1			
33	C. G.	52·1			

TABLE V.—PHENOLS OF BLOOD AND SPINAL FLUID IN EPILEPSY.

	Patient	Age	Sex	Blood phenols mg. per 100 c.c.	Spinal fluid phenols	Spinal fluid phenols. Blood phenols
1.	L. P.	53	F.	1·7	0·55	0·32
2.	J. N.	39	F.	1·3	0·51	0·39
3.	E. R.	22	F.	1·5	0·83	0·55
4.	H. G.	68	F.	1·8	0·71	0·39
5.	A. A.	62	F.	1·6	0·91	0·56
6.	M. L.	56	F.	2·3	0·76	0·33
7.	J. M.	54	F.	2·1	0·64	0·30
8.	M. L.	52	F.	1·6	0·67	0·42
9.	E. McG.		F.	2·3	0·75	0·33
10.	E. B.		F.	1·8	0·61	0·34
			Average	1·8	0·69	0·38

Ling [39] recently adapted the Wu method for plasma proteins to the determination of spinal fluid protein. In our analyses this method has been employed. Spinal fluid proteins were estimated in 50 cases of epilepsy. With his technique Ling found the protein of normal spinal fluid

to vary from 18·8 mg. to 37·9 mg. averaging 25·5 mg. per 100 c.c. Of the fifty cases reported in Table IV, and in Chart II, six give protein figures within normal limits; these, however, approximate the upper normal level. The remaining cases show values from 37·9 to 95·5 mg., the majority being above 50 mg. per 100 c.c. In all the patients reported here, the Wassermann reactions of blood and spinal fluid were negative, and all serological tests normal. Since this method of protein determination is based upon the estimation of tyrosine in the fluid, it is possible that the substances here determined as protein are less complex compounds, such as proteoses, peptones or polypeptides. Such compounds do not give the precipitation tests for protein. The observation made by Cuneo [40] in 1915, that a toxic substance possessing the nature of a proteose is found in the blood of epileptics, and is a factor in precipitating convulsions, is of interest in this connection. Our results suggest the possibility of the occurrence of tyrosine-containing groups, probably complex protein catabolites, in the spinal fluid of the epileptics studied by us.

Ling's colorimetric method for proteins of the spinal fluid includes the use of a reagent originally proposed for phenols by Folin and Denis [41]. Hence it occurred to us that the colour-producing substances in spinal fluid determined by this method might be phenols. Consequently, in ten cases of epilepsy, analyses for total phenols in blood and spinal fluid were made by the method of Theis and Benedict [42]. In a series of twenty-six specimens of normal blood, these authors report figures for total phenols from 1·1 to 2·2 mg. per 100 c.c. It is evident that the total phenols of the epileptic bloods fall within this range. Less total phenol is found in spinal fluid, averaging 38 per cent. of that of the blood. No variation from normal was noted in the amount of total phenols of the blood. Moreover, the average phenol content of the spinal fluid of these epileptics is not sufficient to introduce any error in the protein determinations by Ling's method.

Osnato and Killian [42] have observed an increase in the *lactic acid* of the spinal fluid of two cases of epilepsy, the concentration of lactic acid in the spinal fluid exceeding that of the blood. With the object of accumulating more data on this phase of the metabolism in epilepsy, an intensive study was planned of variations in the lactic acid concentration of the blood and spinal fluid in relation to the sugar concentration and acid-base balance of these fluids, and their apparent bearing upon the clinical course of the disease. Analyses for sugar, both of the blood and spinal fluid, were made according to the technique of Shaffer and Hartmann [44] For lactic acid determinations Clausen's [45] method was utilized for the earlier analyses, but recently Brehme and Brahdy's

[46] modification of Clausen's technique was adopted. Comparative studies of the sugar and lactic acid of the blood and spinal fluid have been made in seventy-five cases of epilepsy. The majority of these patients were inmates of the Manhattan State Hospital for the Insane, and the specimens were obtained under the conditions previously described. Immediate analysis of the material here was particularly important to avoid changes in sugar and lactic acid due to glycolysis. (Nishimura [47], and Katayama [48].)

TABLE VI.—SUGAR AND LACTIC ACID OF THE BLOOD AND SPINAL FLUID IN EPILEPSY.

				Blood		Spinal fluid			
	Patient	Age	Sex	Sugar	Lactic acid	Sugar	Lactic acid	Interval since last seizure	Subsequent seizure
				mg. per 100 c.c.		mg. per 100 c.c.			
1.	A. J.	51	F.	99	12·9	68	31·6	23 days	47 days
2.	K. C.	42	F.	99	28·0	52	29·1	30 days	9 days
3.	S. C.	32	F.	78	28·1	64	46·2	16 days	36 days
4.	R. R.	52	F.	108	45·6	61	34·0	16 days	None for 90 days
5.	M. M.	69	F.	82	35·3	55	41·8	4 days	11 days
6.	L. V.	25	F.	83	53·2	64	78·5	6 days	13 days
7.	S. D.	28	F.	99	79·1	79	43·3	½ hour	12 hours
8.	I. H.	20	F.	84	51·9	55	43·9	6 days	12 hours
9.	G. P.	32	F.	87	42·6	55	32·6	3 days	5 hours
				76	41·4	48	37·7	2 days	Not for 90 days
10.	J. N.	39	F.	87	22·7	52	24·6	6 days	12 days
11.	L. S.	54	F.	124	12·4	69	12·1	54 days	26 days
12.	M. T.	51	F.	92	7·4	64	12·1	30 min.	12 hours
13.	C. G.	29	F.	111	8·8	64	11·3	6 hours	19 days
14.	A. H.	34	F.	92	41·4	52	23·5	30 min.	15 days
15.	M. R.	33	F.	106	33·3	69	31·3	30 min.	1 day
16.	R. McK.	54	F.	99	16·5	48	24·7	3 days	3 days
17.	I. S.	62	F.	87	16·4	58	37·7	1 day	7 days
18.	K. K.	64	F.	79	21·4	72	10·1	1 day	4 days
19.	A. S.	28	F.	89	37·1	76	23·7	1 day	28 days
20.	J. M.	34	F.	—	29·9	—	41·4	8 hours	

TABLE VII.

					Blood		Spinal fluid			
	Date	Patient	Age	Sex	mg. per 100 c.c. Sugar	Lactic acid	mg. per 100 c.c. Sugar	Lactic acid	Ratio Sp. fl. sugar Blood-sugar	Ratio Sp. fl. lactic acid Blood lactic acid
1.	Mar. 31	J. D.	36	M.	89	39·1	61	20·2	0·68	0·51
2.	Mar. 31	P. O.	59	M.	76	34·7	64	22·1	0·84	0·63
3.	Mar. 31	F. B.	54	M.	84	32·1	69	22·7	0·82	0·70
4.	Mar. 31	J. M.	26	M.	79	32·1	66	19·8	0·83	0·61
5.	April 4	H. G.	7	F.	92	23·3	48	20·2	0·52	0·86
6.	April 6	S. G.	3½	M.	95	31·5	64	22·7	0·67	0·72
7.	April 7	R. S.	34	M.	102	37·8	69	18·3	0·67	0·48
8.	April 7	E. S.	54	M.	89	34·0	69	25·8	0·77	0·75
9	April 7	C. B.	24	M.	95	37·8	72	22·7	0·75	0·60
10.	April 7	W. P.	47	M.	76	29·6	64	27·1	0·84	0·91
11.	April 7	W. B.	15	M.	69	49·8	76	38·4	1·10	0·77
12.	April 14	C. L	40	M.	84	29·6	69	24·6	0·82	0·83
13.	April 14	F. B.	54	M.	87	23·9	69	20·8	0·79	0·87
14.	April 14	G. M.	32	M.	87	31·2	61	22·7	0·70	0·72
15.	April 14	J. C.	17	M.	95	29·6	76	23·3	0·80	0·78
16.	April 14	H. M.	23	M.	79	27 7	61	20·2	0·77	0·73
17.	April 21	W. H.	52	M.	87	30·2	72	39·1	0·82	1·28
18.	April 21	A. H.	—	M.	89	26·5	64	71·8	0·72	2·70
19.	April 21	J. E.	—	M.	72	28·4	82	33·4	1·13	1·18
20.	April 26	T. S.	10	F.	87	34·7	55	18·9	0·63	0·54
								Average	0·74	0·70

In Tables VI and VII, data on forty of these cases are presented. All of the subjects reported in Table VI were from the female service, while those of Table VII were from the male service of the institution. Moreover, the lactic acid figures in Table VI were obtained by Clausen's method, whereas the Brehme and Brahdy revision of this method was utilized for the analyses of Table VII. It is significant that the figures demonstrate similar variations in the lactic acid of the body fluids. For the specimens obtained during the interval period, the blood-sugars (Tables VI and VII) vary from 69 to 124 mg. per 100 c.c. The range of normal blood-sugar with the present methods of analysis is from 70 to 100 mg. per 100 c.c. According to these criteria we have observed no instances of hypoglycæmia among epileptics, and but a few instances of mild hyperglycæmia. The variations noted in spinal fluid sugar were from 48 to 82 mg, per 100 c.c. In two instances the spinal fluid sugar exceeded the blood-sugar (Cases 11 and 19 of Table VII). With these two exceptions, the sugar of the spinal fluid had on the average a concentration equivalent to 74 per cent. of that of the blood. Myers and Fine [49] found the sugar of the spinal fluid in nephritis to be 60 per cent. of that of the blood. Patterson and Levi [50] have observed in the study of ten cases of epilepsy a concentration of sugar in the spinal fluid of 50-70 per cent. of that of the blood.

Low blood-sugar values in epilepsy have been reported by Daly, Pryde and Walker [51], and by Cuneo [52]. Our results do not substantiate these findings. Cuneo and Holmstrom [53] observed a rise in blood-sugar immediately after the epileptic seizures. Similar changes were noted in our patients. Subjects 1 and 2 of Table IX are illustrative cases. However, this hyperglycæmia is not a phenomenon specific for epileptic convulsions, since analogous changes have been described after the convulsions produced in animals by strychnine.

The *lactic acid* of normal blood obtained during the fasting state varies from 11 to 18 mg., with an average of 15 mg. per 100 c.c. (Nishimura) In spinal fluid, Osnato and Killian have reported figures from 6·3 to 9·4 mg. per 100 c.c. in four normal individuals and in miscellaneous pathological conditions, excluding infectious diseases, involving the central nervous system, values from 8·6 to 18·0 mg. per 100 c.c. In normal spinal fluid Scheller [54] found from 9 to 15 mg. of lactic acid per 100 c.c. Glaser [55], however, notes a wider variation. For normal spinal fluid he reports 11 to 27 mg., averaging 19 mg. of lactic per 100 c.c. Reference to Tables VI and VII reveals a significant increase in both the lactic acid of the blood and of the spinal fluid in thirty-five of the forty cases reported. In eight instances, the spinal fluid lactic acid exceeds the concentration observed in the blood; in the remaining cases, however, the amount of lactic acid in the spinal fluid forms 70 per cent. of that of the blood.

Liljestrand and Wilson [56] prepared sarcolactic acid from the urine of normal persons after strenuous muscular exercise over a short period of time. After eclamptic convulsions Zweifel [57] isolated sarcolactic acid in considerable quantities from the maternal venous blood and the blood of the umbilical cord of the newborn. In view of the fact, exemplified by the observations of these investigators, that lactic acid is a product of vigorous muscular contractions, it was thought that the increase in the lactic acid of the blood and spinal fluid in epilepsy might be attributed to the convulsions. The intervals elapsing between the previous seizure and the collection of the specimens, and also the interval existing between the collection of the specimens and the subsequent seizure, are recorded in Table VI. It is apparent from reference to this that the level of the lactic acid bears no relation to the previous seizure. Nor is there any demonstrable dependence of the time of the subsequent seizure upon the lactic acid concentration in these fluids. However, in Table IX data are presented showing increases in lactic acid of the blood and spinal fluid from normal values to figures two to three times the normal in specimens obtained from twenty minutes to five hours after the convulsions.

Investigations upon the influence of insulin upon carbohydrate metabolism have shown that lactic acid is an intermediate product in glucose utilization (Briggs, Koechig, Doisey and Weber [58], and Katayama and Killian [59]). Lactic acid may also be produced during the deaminization of amino acids, derived from propionic acid (Lusk [60]). It is significant to note that apparently the increase of lactic acid in the spinal fluid is not at the expense of the sugar of the spinal fluid. In this respect there is evident a definite distinction between the increase in lactic acid in the spinal fluid in epilepsy and in the meningitides. In the latter conditions, Osnato and Killian, Scheller and Glaser find a diminution of the spinal fluid sugar coincident with the rise in lactic acid. The uniform finding of a high level of lactic acid, both in blood and spinal fluid, suggests abnormal metabolic processes in these epileptics. However, if such abnormal metabolic processes exist, they are not of sufficient magnitude to influence either the respiratory quotient or the basal metabolism. Basal metabolic rates determined on the cases studied by us have fallen within the normal range of $\pm$ 10 per cent. The respiratory quotients of eleven children with idiopathic epilepsy were found to vary from 0·77 to 0·85 by Talbot, Hendry and Moriarty [61]. In the series studied by these authors, the basal metabolisms were normal or slightly elevated.

The *reaction of the blood-plasma* in epilepsy has been the subject of numerous reports in the literature. Dautrebaude [62] believes he has

demonstrated an alkaline substance in the blood of epileptics. Bigwood [63] champions the hypothesis that in the blood of epileptics there is a tendency to an alkalosis, and the rising pH of the blood produces a reduction in the blood-calcium ions, since the concentration of calcium ions is diminished with increasing alkalinity. This reduction in calcium ions precipitates the convulsion, and the convulsion in turn diminishes the alkalinity of the blood. Geyelin, Bigwood and Wheatley [64] state that the blood of any given case of epilepsy shows a wider range of reaction than does the blood of a given normal individual. For normals a range in pH of blood-plasma from 7·36 to 7·43 is noted, but for treated and untreated cases of epilepsy the variations ranged from 7·25 to 7·50. The average value for the pH of spinal fluid reported by Patterson and Levi was 7·75. This figure they consider normal, but in some instances figures as high as 8·1 were obtained. Obviously such results do not represent the true reaction of spinal fluid in the body. Since the description by McQuarrie and Shohl [65] of a practical means of collecting spinal fluid for pH determinations, we have utilized this procedure in comparative studies of the reaction of the blood-plasma and spinal fluid in twenty-nine cases of epilepsy. The results are recorded in Tables VIII and IX. McQuarrie and Shohl have shown that the blood and spinal fluid have a normal range for the pH from 7·35 to 7·43 ± 0·02. The carbon dioxide-combining power has been determined upon the plasma collected under oil in all instances, except Case 4, Table VIII, in which the carbon dioxide-combining power was estimated upon oxalated plasma. Determinations of the blood-plasma pH were made by Cullen's method [66].

Patient S. W. (Table VIII, 3) shows an uncompensated alkalosis, both in the blood-plasma and the spinal fluid, due to alkali therapy. Case 1 (Table VIII) presents an unusually high figure for the blood-plasm, a pH 7·50, while the spinal fluid pH is within normal limits. Here it is noted that the difference between the blood-plasma and spinal fluid amounts to 0·10. Apparently the high figure obtained for the blood-plasma was due to loss of CO_2 during the collection of the specimen. In the other cases, the figures for the pH of the plasma range from 7·33 to 7·44 within normal limits. The reaction of the spinal fluid is closely dependent upon that of the blood-plasma, except in Case 5 (Table IX). With this exception the differences in the reaction of the two fluids is within the limits of − 0·02 and + 0·03 pH. There is no evidence presented in these twenty-nine cases of epilepsy studied of a hyperalkalinity of either the blood-plasma or the spinal fluid.

Comparison of the pH of the blood-plasma and spinal fluid obtained after convulsions with the values during the interval period (Cases 11

TABLE VIII.—REACTION OF BLOOD-PLASMA AND SPINAL FLUID IN EPILEPSY.

Patient		Blood-plasma		Spinal fluid	Remarks
		CO_2C.P.	pH	pH	
1. B. H.			7·50	7·40	—
2. W. B.	9/17	62·4	7·42	7·38	—
	9/20		7·47	7·40	—
	4/7	45·7	7·35	7·32	After prolonged seizure
3. S. W.		73·0	7·47	7·48	Na_2CO_3 therapy
4. E. B.		54·1*	7·44	7·45	48 hours after convulsion. On luminal therapy
5. E. R.			7·39	7·50	—
6. A. M.		67 2	7·41	7·42	—
7. P. R.			7 44	7·47	—
8. F. R.		65·5	7·38	7·40	—
9. G. R.			7·38	7·38	After convulsions persisting for 2 hours
10. W. J.	12/8		7·37	7·35	—
	12/11		7·39	7·40	5 hours after convulsion
11. H. V.	12/13	60·7	7·42	7·41	—
	12/20		7·35	7·38	2 hours after convulsion
12. R. M.		61·7	7·36	7·35	—
13. R. H.	1/31	48·5	7·35	7·37	—
	2/7	56·0	7·34	7·35	—
14. K.		57·2	7·33	7·35	—
15. C.			7·37	7·39	—
16. H. S.	3/15	61·7	7·38	7·37	—
	3/23		7·44	7·45	1 hour after convulsion
17. J. S.			7·34	7·37	—
18. H. G.			7·33	7·35	—
19. S. G.			7·36	7·37	—

* On oxalated blood.

TABLE IX.—SUGAR, LACTIC ACID AND pH OF BLOOD AND SPINAL FLUID IN EPILEPSY.

Patient	Age	Sex	Blood				Spinal fluid			Remarks
			Sugar	Lactic acid	CO_2C.P.	pH	Sugar	Lactic acid	pH	
			mg. per 100 c.c.		vol. per cent.		mg. per 100 c.c.			
1. H. V.	14	M.	87	15·4	60·7	7·42	55	15·3	7·41	Epilepsy. Interval
			99	25·1	—	7·35	72	44·5	7·38	2 hrs. after seizure
2. W. J.	33	M.	87	15·8	—	7·37	23	15·4	7·35	Epilepsy. Interval
			102	17·2	—	7·39	55	14·4	7·40	5 hrs. after seizure
3. G. R.	10	M.	65	62·4	—	7·38	Trace	34·7	7·38	Epilepsy. After convulsions for 2 hrs.
4. A. M.	34	M.	—	77·0	67·2	7·41	—	74·6	7·42	Epilepsy. C.-S. lues. Malaria[1]
5. W. B.	15	M.	91	15·6	62·4	7·42	70	12·5	7·38	Epilepsy. Interval
			69	49·8	45·7	7·35	76	38·4	7·32	20 min. after seizure
6. S. W.	14	F.	86	56·8	73·0	7·47	58	63·4	7·48	Epilepsy. $NaHCO_3$
7. E. B.	6	F.	103	18·2	54·1	7·44	71	17·8	7·45	Epilepsy
8. H. G.	7	F.	92	23·3	—	7·33	48	20·2	7·35	Epilepsy. Interval
9. S. G.	3½	M.	95	31·5	—	7·36	64	22·7	7·37	Epilepsy. Interval
10. T. S.	10	F.	87	34·7	—	7·42	55	18·9	7 42	Epilepsy. Interval

[1] This patient had epileptic seizures several years prior to syphilitic infection, which eventually involved the nervous system. The nervous syphilis was treated by malarial inoculation, and following this the Wassermann reaction was negative in the blood and spinal fluid.

and 13 of Table VIII, 1 and 5 of Table IX) reveals a decrease of the alkaline reserve after epileptic seizures. However, this is not uniform, since in two instances (Cases 10 and 16, Table VIII, and 2 of Table IX) the post-convulsive fluids gave higher figures for pH than did the interval specimens. It was expected that the high concentration of lactic acid of the blood and spinal fluid observed in epilepsy would diminish the alkaline reserve of these fluids. In Table IX, however, it is seen that the reaction of the blood and spinal fluid bears no direct relation to the concentration of lactic acid in these fluids. These findings indicate that the spinal fluid has an ample alkali reserve similar to that of the blood-plasma.

Marrack and Thacker [67] report data on the reaction of the blood in thirty-four epileptics. The figures obtained range from 7·12 to 7·47; but with three exceptions they lie within normal limits, although the patients were having frequent seizures. Our observations support their conclusion that a high plasma pH cannot be considered to play an important part in producing fits. Hamilton has observed that the values for total base in spinal fluid are always larger than the sum of the acids determined. In epileptics the average difference is about 12 c.c., 0·1 N, and this amount of base is probably bound by undetermined acid factors. The data presented in Tables VIII and IX suggest that lactic acid is one of the acid radicles combined with the excess base noted by Hamilton.

Summary.

In nineteen cases of epilepsy the blood-serum calcium varied from 9·5 to 12·1 mg. per 100 c.c., averaging 10·94 m.g. per 100 c.c. In these cases the calcium of the spinal fluid ranged from 5·0 to 6·3 mg. per 100 c.c., averaging 5·68 mg., 51 per cent. of the blood-serum calcium. The inorganic phosphorus of the blood-serum of eleven cases of epilepsy fell within the limits of 2·7 and 4·5 mg., the average being 3·51 mg. per 100 c.c. In the spinal fluid of the same patients the inorganic phosphorus varied from 1·2 to 1·9 mg., with an average value of 1·59 mg. per 100 c.c. The inorganic phosphorus in the spinal fluid was about 45 per cent. of that of the blood-serum.

One patient with epilepsy during the interval period gave an unusually low blood-cholesterol of 0·093 per cent. Twenty-one had figures varying from 0·125 to 0·171 per cent., averaging 0·140 per cent. Only traces of cholesterol were found in the spinal fluid.

With Ling's colorimetric method, six epileptics were found to have spinal fluid protein slightly below the upper normal limit of 37·9 mg. per 100 c.c. Forty-four gave figures from 37·9 to 95·5 mg. per 100 c.c.,

the majority above 50 mg. Since these fluids gave normal precipitation tests, it is possible that these spinal fluids contain simpler tyrosine-containing compounds than protein.

In ten cases of epilepsy, the total phenols of the blood average 1·8 mg., and of the spinal fluid 0·69 mg. per 100 c.c.

The blood-sugar in epilepsy was found to vary within normal limits. Specimens of blood and spinal fluid obtained after epileptic seizures showed an increase in sugar above that noted in the interval period. In two instances in a series of sixty-nine cases, the spinal fluid sugar exceeded the level of blood-sugar, in the remainder the sugar concentration of the spinal fluid averaged 74 per cent. of that of the blood.

A uniform increase was noted in the lactic acid of the blood and spinal fluid in the interval specimens of seventy-five epileptics. This increase was not due to the muscular exertion during convulsions. It may, however, indicate abnormal metabolic processes.

The pH of the blood-plasma and spinal fluid in twenty-nine cases of epilepsy was found to lie within the normal range. The high concentration of lactic acid in the blood and spinal fluid in the cases studied did not change the reacton of the blood or spinal fluid outside of normal limits.

DISCUSSION.

Dr. OSNATO added that some authors had recently advanced the idea that in epilepsy one was dealing with the exact opposite of the group of circumstances which controlled the situation of diabetes. The work recorded here showed that this could not be, as the insulin convulsions were accompanied, perhaps caused, by intense hypoglycæmia, whereas in epilepsy this did not occur.

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CHEMICAL STUDIES BEARING ON THE FORMATION OF CEREBRO-SPINAL FLUID.

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FOR the purpose of this paper the view is taken that cerebro-spinal fluid is formed at the choroid plexus, receives minute additions from the perivascular spaces as it passes over the surface of the brain and spinal cord, and is absorbed through the arachnoid villi into the cerebral venous sinuses. Absorption by way of the lymphatic system of the nerve sheaths is negligible. The experimental evidence on which this view is based needs no reiteration, since it has been reviewed within recent years by Cushing [1] in his Cameron lecture and by Weed [2], two workers who by their own brilliant contributions have done much to lay the foundations of our knowledge of this subject.

With the development of modern microchemical methods, it was but natural that more attention should be drawn to the chemistry of the fluid. In this paper some of the results which I have obtained and their bearing on both physiological and pathological problems will be briefly summarized.

The "meningitis" law.—The question which first engaged my attention was: Granted that the cerebro-spinal fluid is formed by the choroidal epithelium, is there any chemical evidence of the contribution of the nervous system proper to its formation?

Of the products of hydrolysis of lipoids *in vitro*, choline had received most attention as an index of nerve-tissue degeneration. The results were contradictory and as post-mortem specimens of fluid had been used they were difficult to interpret [3]. Less work had been carried out on the phosphate content of cerebro-spinal fluid because large amounts of fluid were required for accurate estimation by methods then known. Using a modification of the Bell-Doisy method, I examined over 150 fluids and sera. The results have been given in an earlier paper [4]. Here I wish to direct attention to a few conclusions of present interest:—

(1) The normal inorganic P content of cerebro-spinal fluid lies between 1·25 and 2 mg. per 100 c.c.

(2) In sixteen cases of acute epidemic encephalitis—no variation from the normal was found.

(3) In meningitis of all types—there is a marked increase in the inorganic P (*vide* diagram).

(4) In chronic organic nervous disease the values found are within the normal limits.

Briefly, in both acute and chronic degenerative nervous disease no increase of inorganic P is found in the cerebro-spinal fluid, whilst in meningitis—tuberculous, meningococcal, pneumococcal, &c.—a marked increase is found.

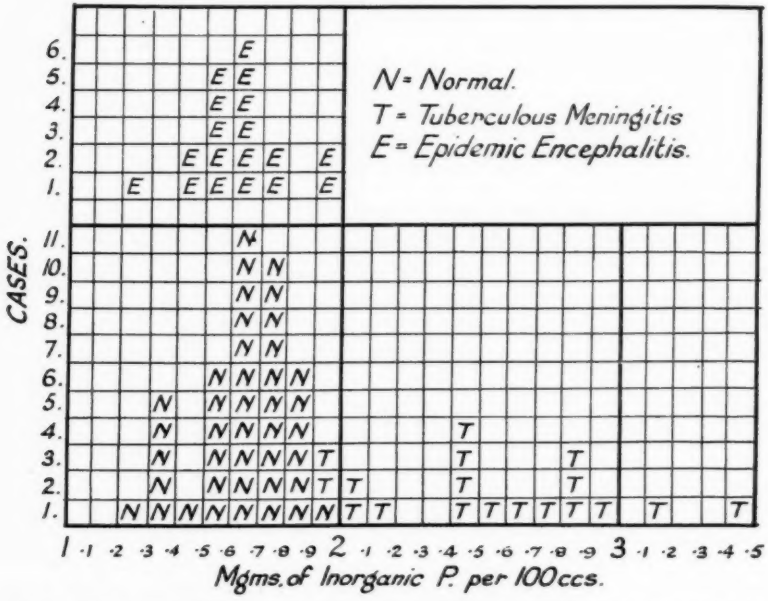
N = Normal.
T = Tuberculous Meningitis
E = Epidemic Encephalitis.
CASES.
Mgms. of Inorganic P. per 100ccs.
1 ·1 ·2 ·3 ·4 ·5 ·6 ·7 ·8 ·9 2 ·1 ·2 ·3 ·4 ·5 ·6 ·7 ·8 ·9 3 ·1 ·2 ·3 ·4 ·5

FIG. 1.—In the above figure the abscissæ represent mg. of inorg. P. per 100 c.c of fluid; the ordinates, number of cases. Thus eleven normal cases (N) had between 1·6 and 1·7 mg. A glance at the figure shows that in acute epidemic encephalitis the values obtained correspond with the normal values; the increase found in tuberculous meningitis is strikingly illustrated.

Our first problem then was the explanation of this rise in the inorganic P content of cerebro-spinal fluid in meningitis. This was shown to be independent of the blood-plasma inorganic P, the cell and protein content of the cerebro-spinal fluid, the age of the patient, the proximity of death, repeated lumbar puncture, &c. The possibility of lecithin disintegration, due to an associated encephalitis playing an essential part in the rise, was rendered extremely improbable by a consideration of the following data :—

(1) One grm. of lecithin contains approximately 40 mg. P.; 1 grm. of brain tissue contains 6 per cent. lecithin, i.e., 2·4 mg. P; thus, if the normal volume of cerebro-spinal fluid be taken as 150 c.c., the rapid and complete disintegration of 1 grm. of brain-tissue would be necessary to increase the inorganic P content of cerebro-spinal fluid by 1·6 mg. per cent.

(2) Complete disintegration of lecithin with liberation of free PO_4 ions is necessary before the phosphorus can be estimated as inorganic.

(3) There is no increase of inorganic P in acute epidemic encephalitis.

(4) Only a small amount of nerve tissue would be involved, and this gradually over a relatively long period.

The hypothesis advanced in explanation of the rise is based on the altered permeability of the cells of the choroid plexus and cerebral vessels in inflammatory states. These cells form a living membrane which separates arterial blood from the cerebro-spinal fluid. The permeability of this membrane is "selective," so that the composition of cerebro-spinal fluid under normal conditions remains constant. For the purposes of my argument it will be useful to consider the following table:—

	Normal		Meningitis
	Blood plasma	Cerebro-spinal fluid	Cerebro-spinal fluid
Group I— (Substances normally present in greater quantity in the plasma than in the fluid)	Protein .. 6-7 per cent. Inorg. P .. 2-4 mg. per cent. Uric acid .. 2-4 ,, ,, Cholesterol 150 ,, ,, Calcium .. 10 ,, ,, Sulphates .. 4 ,, ,, Glucose .. 100 ,, ,,	Trace .. .. 1·25-2 mg. per cent. Trace .. .. ,, ... 5-6 mg. per cent. 1 ,, ,, 50-80 ,, ,,	Increase ,, ,, ,, ,, ,, Increase in early stage; decreased later
Group II— (Substances normally present in greater quantity in the fluid than in the plasma)	Chlorine .. 560-620 mg. per cent. (as NaCl)	725-750 mg. per cent.	Decrease
Group III— (Substances which either naturally or after injection are present in the plasma, but normally do not pass into the fluid in any but the most minute traces)	Fibrinogen .. .. Iodides .. .. .. Salicylates .. .. Nitrates .. .. .. Sod. fluorescein (uranin) Agglutinins (meningococcal) Bile pigments .. .. Organic arsenic, &c. ..	All these have been shown to pass into the cerebro-spinal fluid in meningitis	

Should the barrier between blood and cerebro-spinal fluid be damaged so that its "selective" permeability is impaired, then there should be

an increasing concentration of substances in Groups I and III in the cerebro-spinal fluid, whilst the only member of Group II will diminish in the cerebro-spinal fluid. *All these changes have been shown to occur in the cerebro-spinal fluid in meningitis*, and have led me to adopt the view that the main factor influencing the chemical composition of cerebro-spinal fluid in meningitis is the degree of damage to the cells of the choroid plexus and cerebral blood-vessels by the invading virus or toxin. This impairs the vitality of these cells, increases their permeability, and thus causes *the cerebro-spinal fluid in meningitis to approximate to the blood-plasma in chemical composition*. In the case of assimilable foodstuffs, as glucose, the quantity is decreased in the later stages owing to increased utilization by the bacterial cause of the meningitis, the cell exudate and the inflamed cells of the choroid plexus itself.

Some recent studies in the magnesium content of the cerebro-spinal fluid offer striking support of this view [5]. Magnesium is unique amongst the metallic ions, in that more is present in the cerebro-spinal fluid (3 to 3·6 mg. per cent.) than in the plasma (2 to 3 mg. per cent.). If the general law above enunciated be sound, then the excess of magnesium normally present in the cerebro-spinal fluid should become less marked or disappear in meningitis, as in the case of the chlorine ion. In the non-meningitic cases (omitting a doubtful case of encephalitis) the most and least marked differences between plasma and cerebro-spinal fluid were respectively 1·17 mg. and 0·47 mg. per cent. In the meningitic cases these were 0·11 mg., and – 0·62 mg. per cent. respectively, i.e., in the latter case more magnesium was present in the plasma than in the cerebro-spinal fluid, striking testimony to the validity of the general law.

The effect of withdrawing cerebro-spinal fluid on the composition of the blood-plasma.—Whilst investigating whether a rise in the magnesium content of the plasma was followed by a similar rise in the cerebro-spinal fluid, results were obtained which suggested that the withdrawal of 10 to 15 c.c. of cerebro-spinal fluid was itself followed in many cases by chemical alterations in the blood-plasma.

If 10 to 20 c.c. of 10 per cent. solution of $MgSO_4$ in water be injected intramuscularly, a rise in the magnesium content of the serum occurs, reaching a maximum in one and a half to two hours, and returning to normal within six hours; e.g., in a patient with 2 to 3 mg. per cent. Mg in his serum, 20 c.c. of 10 per cent. $MgSO_4$ cause the Mg to rise to 4·3 mg. per cent. in two hours. In no case was it possible to demonstrate that this rise of magnesium was reflected in the cerebro-spinal fluid, but it was noted in many cases that the second lumbar puncture was followed by a rise in the magnesium content of the serum, e.g:—

W. J., male, aged 18. Post-encephalitic Parkinsonism, with marked bradykinesia and tremor.

	Time	Time after injection of $MgSO_4$	Magnesium content (in mg. per 100 c.c.) of	
			Serum	Cerebro-spinal fluid
Blood taken	10.25 a.m.	—	2·60	—
Cerebro-spinal fluid taken (lumbar puncture)	10.30 ,,	—	—	3·19
2 grm. of $MgSO_4$ in 20 c.c. aq. injected into right buttock and massaged	10.35 ,,	—	—	—
Blood taken	12.5 p.m.	1 hour 30 min.	4·24	—
,, ...	12.35 ,,	2 ,, 0 ,,	2·88	—
,, ...	1.10 ,,	2 ,, 35 ,,	2·90	—
,, ...	1.28 ,,	2 ,, 53 ,,	2·90	—
Cerebro-spinal fluid taken (lumbar puncture)	1.30 ,,	2 ,, 35 ,,	—	3·23
Blood taken	2.10 ,,	3 ,, 35 ,,	**3·44**	—
,, ...	3.7 ,,	4 ,, 32 ,,	2·88	—
,, ...	4.35 ,,	6 ,, 0 ,,	2·64	—

In further experiments it was shown that :—

(1) Withdrawal of 10 to 15 c.c. of fluid was followed normally in many cases by a slight but definite rise in the magnesium content of the serum ; and

(2) Lumbar puncture alone, without any fluid being withdrawn, was unaccompanied by this rise.

The interpretation of these facts is by no means simple. I have been able to show that the injection of pituitary extract (posterior lobe) is followed, in many but not all cases, by a rise of similar type in the magnesium content of serum ; other glandular products failed to produce this rise. It is, therefore, most probable that the withdrawal of cerebro-spinal fluid and consequent lowering of pressure allows a more rapid passage of the active principle of the pituitary gland into the fluid ; this rapidly passes into the plasma, where it produces its characteristic effect on the magnesium content.

In this connection the similar effects produced by cerebro-spinal fluid withdrawal and by injection of the extract of posterior lobe of pituitary in controlling the polyuria of diabetes insipidus are of interest, and support the interpretation above offered [6], [7], [8].

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DISCUSSION.

Dr. F. FREMONT-SMITH (Boston, Mass., U.S.A.): It gives me pleasure to be able to agree in the main with Dr. Cohen's conclusions. Certainly the relation between plasma and cerebro-spinal fluid is complex, both because the plasma is a heterogeneous mixture whose exact composition and state is not yet completely understood, and because the cerebro-spinal fluid is separated from arterial plasma by one membrane, the choroid plexus, and from venous plasma by quite another, composed of the arachnoid villi. Nevertheless, certain significant facts are clear: the plasma and cerebro-spinal fluid, although differing markedly in composition from one another, have essentially the same total osmotic pressure, and the rate of formation and absorption of the cerebro-spinal fluid may be varied at will by modifying either the osmotic or the hydrostatic pressure of the blood. From these considerations we cannot escape the conclusion that dialysis (which is but a special form of diffusion) is dominant in the formation of the cerebro-spinal fluid. Once this is accepted, the problems of intracranial pressure and cerebral circulation are placed upon a foundation from which quantitative description should be possible.

In regard to the Donnan membrane equilibrium, we are in a position neither to affirm nor to deny its quantitative application to the observed distribution of electrolytes between plasma and cerebro-spinal fluid, because of the lack of certain necessary data. I refer to our ignorance both of the "free water" content of plasma and of the value of the activity coefficient of any of the various ions present. These terms are necessary to the accurate calculation of the Donnan ratio.

That the Donnan membrane equilibrium plays a significant rôle wherever two fluids are separated by a membrane which is permeable to some but not to all of the ions present, we cannot doubt. The high content of chloride ion in the cerebro-spinal fluid we believe is related to the impermeability of the choroid plexus to the protein ion. It should be noted that all body fluids, formed by dialysis or transudation, contain less protein and more chloride than the plasma, the excess of chloride in the fluid being roughly proportional to the excess of protein in the plasma. Such are the aqueous and vitreous humours, œdema fluid, lymph, hydrocele fluid, pleural, peritoneal and synovial effusions. In all these the Donnan membrane equilibrium is undoubtedly implicated.

Dr. Cohen has emphasized the important changes in the cerebro-spinal fluid in meningitis. That these changes indicate increased permeability of the choroid plexus is evident from his data. We must not forget, however, that changes in the composition of the plasma will also modify the composition of the cerebro-spinal fluid. Such changes in the plasma occur in acute and tuberculous meningitis regularly and to a striking degree, and often abruptly. They must not be neglected in evaluating the relative importance of the increase in permeability of the choroid plexus. In all forms of acute meningitis, and most strikingly in tuberculous meningitis, there is a marked drop in the plasma

chlorides, often to less than 400 mg. per 100 c.c. (normal = 570 to 620 mg. per 100 c.c.), which is accompanied by a more or less parallel fall in cerebro-spinal fluid chlorides. I have found the low cerebro-spinal fluid chlorides in these cases to be far more dependent upon the fall in plasma chlorides than upon the increased permeability of the choroid plexus. That a similar drop in both plasma and cerebro-spinal fluid chlorides occurs also in such acute infections as pneumonia and typhoid fever (in the absence of meningitis), as well as in acute intestinal obstruction, bears out this view. It is only when the protein content of the cerebro-spinal fluid is enormously increased, as below a spinal subarachnoid block due either to meningitis or a tumour, that I have found the ratio between spinal fluid and plasma chlorides to be greatly disturbed. Here, without doubt, the grossly increased permeability of the meningeal vessels becomes a significant factor.

The equilibrium between cerebro-spinal fluid and plasma, although complicated, is probably the least complex of any of the equilibria in the body of which quantitative study may be readily made. It is peculiarly fortunate that we should have available one fluid in equilibrium with the plasma, from which protein is almost completely excluded. Further knowledge of this equilibrium will increase our understanding of fluid exchange throughout the organism.

PRODUCTIVE ENDARTERITIS OF THE SMALL CORTICAL VESSELS IN SEVERE TOXÆMIAS.[1]

BY N. W. WINKELMAN, M.D.
(*Philadelphia*),
AND
JOHN L. ECKEL, M.D.
(*Buffalo*).

In 1904 Nissl [1] and Alzheimer [2], under the title of "Endarteritis Syphilitica of the Small Cortical Vessels," described in syphilis a rare change limited to the small vessels of the pia and cerebral cortex. In this condition there occur a swelling and proliferation of the cells of the intima particularly, and to a less degree of the adventitia. Normally the lining of the cerebral vessels consists of but a single layer of flat endothelial cells, but as a result of the syphilitic process the cells proliferate, their nuclei swell up, becoming round instead of oval, and take stains less deeply; mitotic figures, while not common, occur. There is rarely exfoliation of cells, but as a result of narrowing of the lumen complete occlusion of the vessel may develop. When this occurs secondary changes, as partial or complete softening, result. Budding of vessels is present, resulting in new vessel formation and "Paketbildungen" have been described. While the adventitial cells take part in this condition to a slight degree, the elastica and media remain passive. Fatty infiltration is rarely found except in the later stages. These pioneer observations have been confirmed in syphilis by Jacob [3] and Spielmeyer [4].

It has been repeatedly shown that, unlike other syphilitic conditions of the central nervous system, this vessel change is probably toxic and not directly bacterial in origin, because spirochætes have never been found in these cases. It is worthy of note that inflammatory changes are likewise absent.

Similar proliferative vascular changes have been described in certain toxic and infectious conditions, non-syphilitic in nature; it has been produced by experimental poisoning in animals with various drugs, as by lead in toxic doses. Bonfiglio [5] was able to study thickening and

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overgrowth of the endothelium so marked as to produce occlusion of the lumen in some of the smaller vessels. As a rule this condition was limited to the cerebral cortex. Regressive changes were found in the later stages, resulting in the shrinkage and fading of the nuclei and fat droplets in the cytoplasm. This work substantiated that done by Jores [6], in 1902, in rabbits.

In the human, Mott [7] has described the chronic form, and Hassin [8] the acute changes in lead poisoning which resemble to a marked degree that found in the experimental animal, but it was much more diffuse. Arsenic (Weygandt, Jacob and Kofka [9]); manganese, (Lewy and Tiefenbach [10]); carbon monoxide (Herzog [11] and Stewart [12]); and mercury, have been known to produce similar productive changes in the small vessels without evidences of inflammation. It is not common in the acute infections but has been observed in typhoid and typhus (Spielmeyer [4] [13]); experimental dysentery (Lotmar [14]); pernicious malaria (Cerletti [15]); and tuberculous meningitis (Askanazy [16]).

During the past winter we were struck by the similarity in pathological findings in two young individuals. In both cases we found marked productive endarteritis of the small vessels, especially in the cerebral cortex, with minute areas of incomplete softening, very similar to the condition described by Nissl [1] and Alzheimer [2] in syphilis. In reviewing the clinical histories it was found that in the first case the fatal illness came on as a result of eating meat that had produced death in four other individuals. In the second case, while the patient himself had attributed his condition to a food indiscretion, his clinical course was not unlike uræmia. In neither case was there clinical or laboratory evidence of syphilis.

Report of Cases.

Case 1.

Clinical History.—E. J., a coloured girl, aged 7, was admitted to the Philadelphia General Hospital, September 13, 1926, in service of Dr. Le Boutillier, with the history of having eaten some Hamburger steak given to her family by a neighbour. Both families partook of this meat, and shortly after its ingestion all became acutely ill with signs and symptoms of a severe gastro-enteritis, associated with vomiting, diarrhœa and severe pains through the abdomen and legs. The neighbour and three other members of our patient's family died shortly as a result. Our patient was removed to the hospital because of suspected "ptomaine" poisoning.

There were present on admission at this time severe abdominal pain, marked diarrhœa, leg pains, great prostration, rapid pulse and a temperature of 100° F.

She appeared very toxic and cried out upon the slightest attempt to move her. Her eyes were injected. The pupils were equal and reacted normally. The eye movements and eye grounds were normal. There was no ptosis and no double vision. The mouth and tongue were swollen and hyperæmic. There was generalized tenderness of the abdomen with a slight enlargement of the liver, but no distension. The lower extremities were hyperæsthetic. No swelling of the feet was observed. The tendon-jerks of the upper extremities were present, equal and normal, while those of the lower limbs were absent

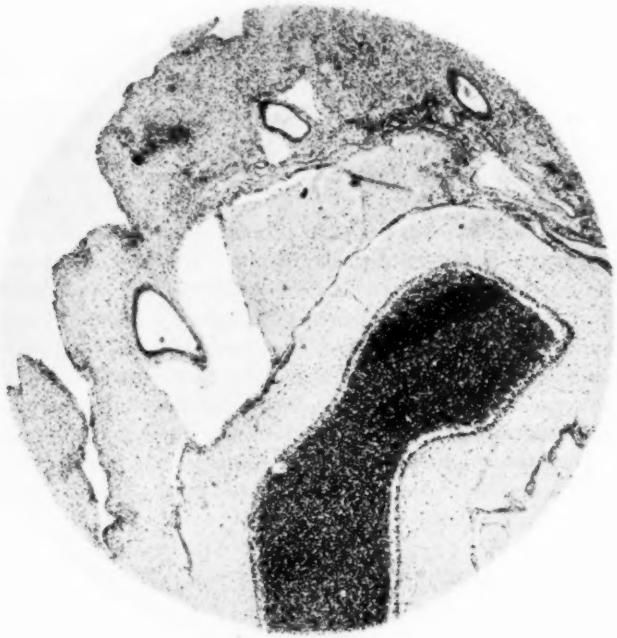

FIG. 1.—Meningeal reaction around cerebellum.

There was neither clonus nor Babinski. Sensation was intact. Treatment was directed toward elimination through the intestinal tract, and in addition supportive measures to combat the marked toxicity and weakness were attempted. For a time she appeared to improve and even partook of soft food. During the second week she began to grow worse. Decubitus set in, the toxic symptoms increased and she gradually became increasingly stuporous, so that nasal tube feeding became necessary. Cortical irritative phenomena in the way of twitchings and jerkings of various muscle groups occurred. Her

temperature gradually rose to 104° F. The pulse-rate increased to 120 and respiration to between 25 and 30 per minute. She became incontinent, the stupor increased and prostration was profound. She failed rapidly and died on the twenty-eighth day of her illness.

Laboratory findings.—The urine was examined repeatedly and at no time showed anything abnormal. Special tests for arsenic gave normal results. The white blood-count varied from 12,800 to 18,400 cells, with the differential count showing 74 per cent. polynuclear cells, and 26 per cent. small and large

FIG. 2.– Marked meningeal infiltration with phagocytic cells. Lymphocytes present in minority.

lymphocytes, but no eosinophils. The hæmoglobin varied from 14·6 to 15·1 grm. per 100 c.c. (normal 15·6 grm. per 100 c.c.). Examination of the fæces was negative for *Bacillus botulinus*. The spinal fluid was clear, under normal pressure, and contained two cells per c.mm. There was a faint trace of globulin and a negative Wassermann reaction in all dilutions. The blood Wassermann was also negative.

Pathology.—Examination of the body revealed nothing except hæmorrhagic involvement of the intestinal tract. Microscopical examination of the various

organs of the body showed cloudy swelling and congestion throughout. The intestinal tract presented in addition inflammatory and hæmorrhagic manifestations.

Brain and spinal cord.—The brain weighed 1,150 grm. The dura was normal. The pia-arachnoid was definitely hazy over the convexity and at the base of the brain. The brain substance appeared paler than usual, the convolutions were broad and flattened. The basal vessels were thin and collapsed. On frontal section no gross abnormalities could be discovered except a

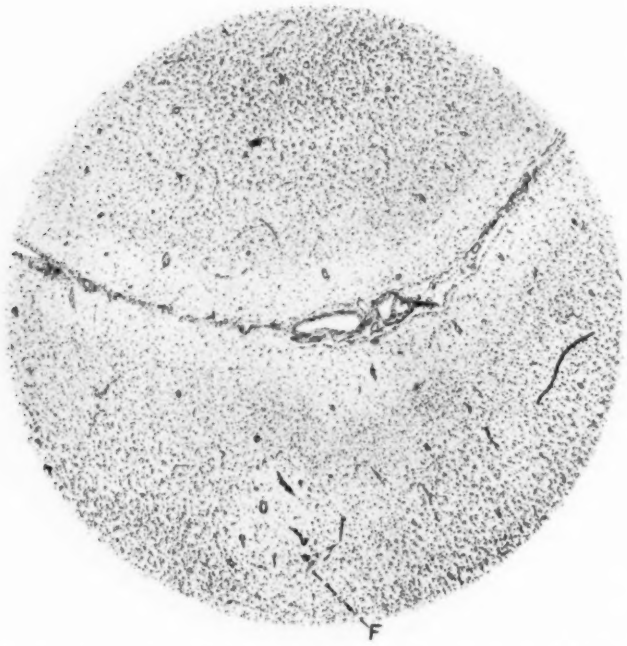

FIG. 3.—Low-power view showing (1) prominence of small vessels, (2) infiltration in meninges, and (3) focus (F).

generalized œdema. The spinal cord was very œdematous but otherwise showed nothing of note. Large sections of the fresh tissue from all areas of the brain and cord were placed in 80 per cent. alcohol for twenty-four hours and for three weeks in 95 per cent. alcohol. The rest of the material was preserved in formalin.

After fixation the following staining methods were used. On the alcohol-fixed material, toluidin blue, van Gieson, Klarfeld and Biondi. Bielschowsky's method, Cajal's gold sublimate, Hortega's first and fourth variants, and fat stains were employed on the formalin material.

Microscopic examination. Pia-arachnoid.—Over the cerebellum (fig. 1), motor, and occipital areas (fig. 2), it was thickened owing to hyperplasia of the fixed tissue elements, œdema and the presence of large, round cells with considerable cytoplasm; these were phagocytic, and many of them still contained foreign material. Lymphocytic cells were rare. There were neither changes in the walls nor infiltration of the large or small vessels within the pia. While the above was the predominating finding, many areas of the brain showed a fairly normal covering.

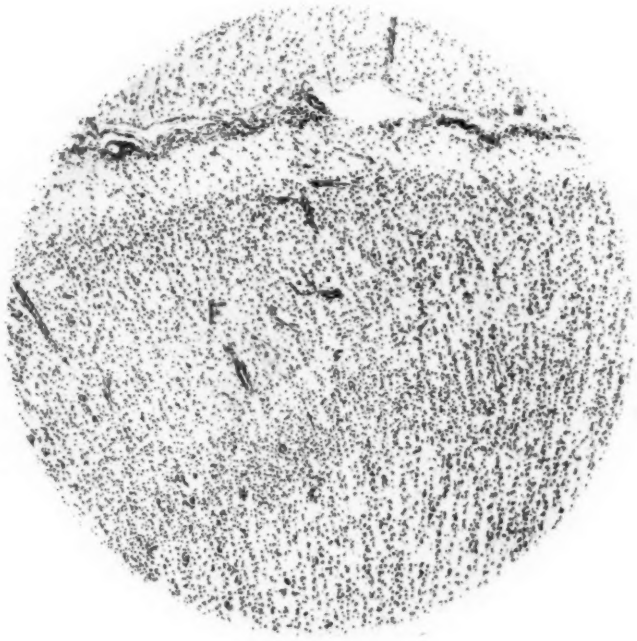

FIG. 4.—Cortex showing (1) meningeal infiltration, (2) focus (F), and (3) small vessel wall prominence.

Cortex.—It was in the motor and occipital areas that the changes to be described reached their height, but many areas of the cortex showed nothing that could be interpreted as abnormal. In affected areas the striking feature was the marked prominence of the small vessels, with an occasional small area of partial softening (figs. 3 and 4) (Verödung instead of Erweichung). The lining cells of the small vessels stood out prominently; they were swollen and vesicular, stained less intently and projected into the lumen. The proliferation of cells was indicated by occasional mitotic figures (fig. 5). New vessel formation was quite evident (fig. 6). The adventitial cells remained practically

passive. Areas of degeneration were for the most part small and limited to the distribution of a vessel (fig. 7); in them a few gitter cells were present. Vascularization was, however, already taking place, as shown by the abundant vessels and evident budding of vessels (fig. 8). Round-cell infiltration was absent. The ganglion cells outside the areas of softening showed loss of Nissl substance, but no evidence of a severe degeneration. Glial increase was evident, especially the astrocytic form. Fat was present in the adventitial and subarachnoid spaces, but was not found within the ganglion cells or in the cells of

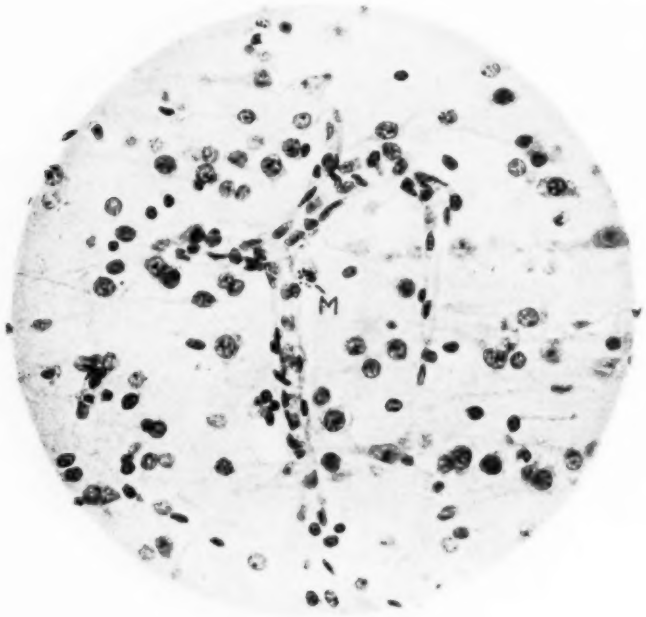

FIG. 5.—Vessel showing swelling and prominence of endothelial cells. Mitotic figures seen at M.

the intima. The cerebellum, brain-stem, basal ganglia and spinal cord showed nothing of note.

Summing up, therefore, the changes found were those of a productive endarteritis of the small cortical vessels with new vessel formation, similar to that described by Nissl and Alzheimer in syphilis as endarteritis syphilitica of the small cortical vessels with areas of partial softening, the result of cutting off of the blood-supply. The pia-arachnoid, especially in places, contained numerous phagocytic elements and showed fibroblastic proliferation.

SUMMARY.—*Case* 2.

Clinical history.—W. N., a 23-year old coloured man, an asphalt worker, was admitted to the Philadelphia General Hospital, in the service of Dr. Piersol, on November 29, 1926, with the complaint of "swelling all over." He stated that on November 1, 1926, he partook of some "bootleg" whiskey and ice-cream. One hour later there began severe pains in the epigastrium and vomiting. He was given large doses of vinegar and soda, which induced vomiting; he improved

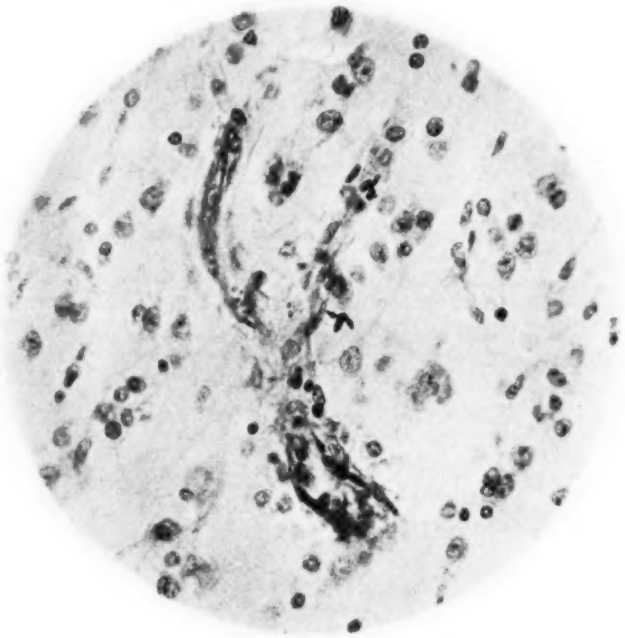

FIG. 6.—Blood-vessel with swelling of endothelium and new vessel formation.

following this, but did not make a complete recovery. Two weeks later, after eating some pork, he again developed severe abdominal pain, with vomiting and diarrhœa. In addition to the gastro-intestinal symptoms, he noted decrease in the quantity of his urine and the development of a gradual swelling over the entire body. He complained of headache and of tenderness and pain in the extremities.

Examination.—On admission to the hospital he impressed one as being very ill. He was drowsy and when aroused was irritable. There was œdema of the face, arms and legs. His pupils were somewhat irregular but reacted normally. The eye movements and vision were normal. The eye-grounds showed no

defects. The mouth was moist, tongue coated and the gums bled freely. The heart was not enlarged and the sounds were not accentuated. The abdomen was tender and tympanitic. The liver was somewhat enlarged. The tendon reflexes of both upper and lower extremities were present, equal, normal, and there were no abnormal toe signs. The extremities were tender to pressure, particularly over the nerve trunks. During his stay in the hospital he voided small amounts of urine, vomited frequently, and had attacks of hiccoughs. His blood-pressure was 170 systolic, 115 diastolic, during the first month. Under

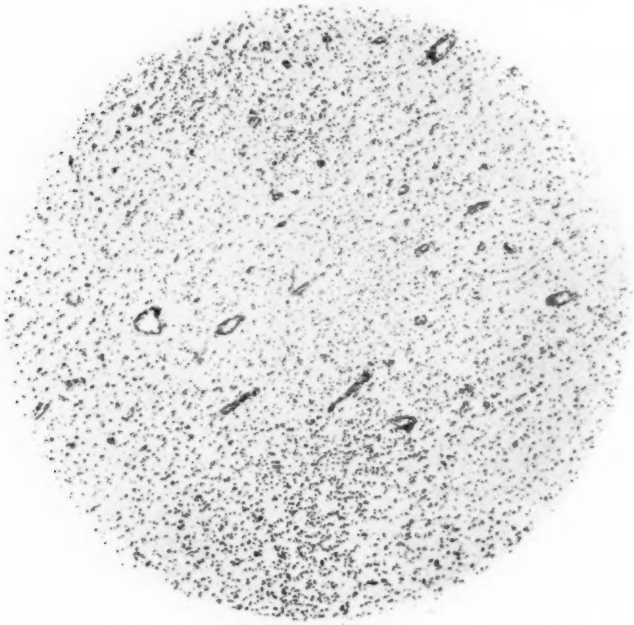

FIG. 7.—Cortex showing enormous destruction of cortical tissue, with marked changes in the small vessels.

diuretics, hot packs, hypodermoclysis, venesection and spinal tappings, he gradually improved to January 18, 1927, when suddenly he developed convulsions, general in character, which lasted off and on for twenty-four hours. During the height of these convulsions his blood-pressure rose to 220 systolic, 110 diastolic. A spinal drainage was done, 30 c.c. of fluid being removed. Following this he improved for about one week and remained mentally alert, though he vomited occasionally. On January 31, 1927, he had a second series of general convulsions, lasting twenty minutes, after which he vomited. He then gradually lapsed into stupor and died February 7, 1927.

Laboratory findings.—The urine on many occasions showed considerable albumin with hyalin and granular casts and leukocytes. The specific gravity varied from 1016 to 1020. The blood-urea upon admission was 22 mg. per 100 c.c., and this gradually rose on each successive examination, until just before death it had risen to 110 mg. per 100 c.c. The white blood-count varied from 11,700 to 16,500 cells. The differential count was 72 per cent. polynuclear cells, 22 per cent. small and large lymphocytes and 3 per cent. transitional cells. No eosinophils were found. The Wassermann test of the blood-serum was

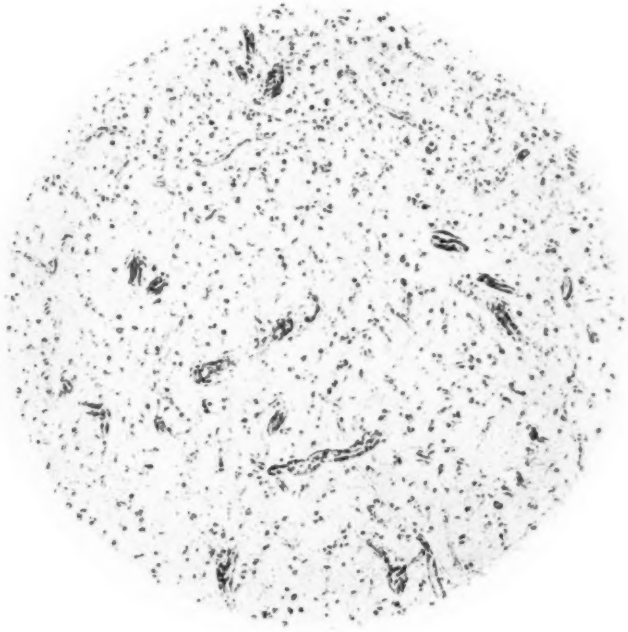

FIG. 8.—Focus with vascularizations.

negative in all antigens. Spinal fluid examination revealed neither cell increase nor globulin. The Wassermann test was negative in all dilutions. Special tests for arsenic in the urine were negative. His phenolsulphonephthalein test showed but 8 per cent. return of the dye in two hours. The icterus index was normal. The stools contained no ova, parasites or blood. The final creatinin determination was 5·5 mg. per 100 c.c.

Pathology.—Examination of the various organs of the body showed marked cloudy swelling, and in addition there was present a chronic glomerular nephritis with an acute nephrosis superadded. The intestinal tract showed areas with hemorrhage in both the mucosa and the submucosa. The aorta was normal.

Brain.—The weight of the brain was 1,200 grm. It was definitely paler than normal. The pia-arachnoid over the vortex showed a slight clouding, while at the base it was thickened and milky. The basal vessels were small, their walls were slightly thickened; no plaques were seen. On frontal section of the brain no gross abnormalities were made out. Large sections were immediately taken from representative areas of the entire brain and placed in 80 per cent alcohol; the rest was fixed in formalin. Similar stains were used in the examination of this case as in Case 1.

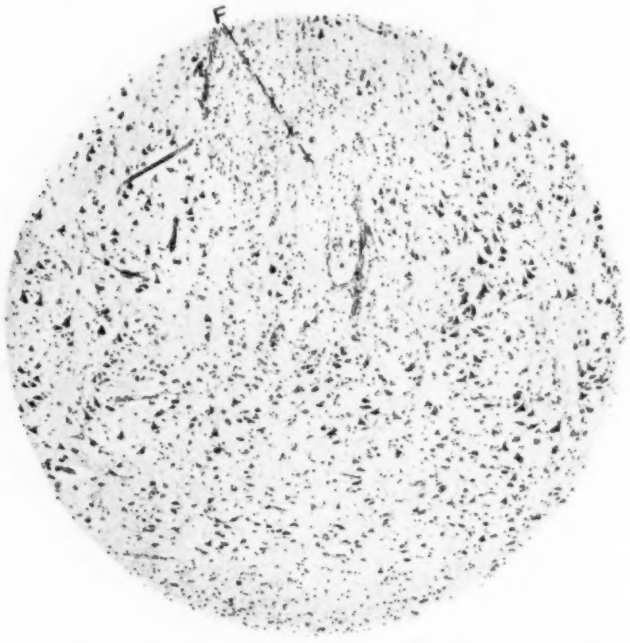

FIG. 9.—Cortex showing focus (F) of "Verödung," with loss of ganglion cells and increase of glia. Prominence of vessels is a feature.

Microscopic examination.—The pia-arachnoid showed hyperplasia and œdema, with collections of cells of the phagocytic type scattered throughout. The larger pial vessels showed but little change, but the endothelial cells of the smaller ones were swollen. They were surrounded in places by collections of phagocytic cells within their adventitial spaces.

Cortex.—The general cyto-architecture was normal, with the exception of small irregularly scattered foci of softening (fig. 9), in which the ganglion cells had disappeared and vascularization and glial proliferation had occurred. The ganglion cells outside these foci were small and atrophic, taking the stain

(toluidin blue) heavier or more intensely than is normal. Irregularities in cell outline were present and tortuosity of the axones could be seen. A striking feature of the cortex was the prominence of the very small vessels because of the endothelial and, to a less extent, adventitial proliferation. New vessel formation could be seen. In some of the vessels in which the condition was apparently older, the lining cells were shrunken and irregular in outline. Their cytoplasm contained fat droplets. Inflammatory changes were completely absent.

The above changes, while not entirely limited to the cortex, were present in a much smaller degree in the brain-stem, cerebellum and basal ganglia. In the cortex the disease had no site of predilection, but was scattered fairly uniformly. As compared with our first case, this one showed more chronic changes; the process here lasted over three months, in contrast to one month in the first case.

Remarks.

We have here described two cases of productive endarteritis, both of which occurred in young, non-syphilitic individuals. In Case 1 the symptoms followed directly the ætiological factor, tainted meat, which was responsible for similar symptoms in five other individuals, of whom four died. In this case the cerebral changes were seen in their active formative stage, as budding and mitotic figures were present. Here the affection was limited to the cortex, and in the cortex it was not uniform but predominated in the occipital and motor areas. Secondary changes had already occurred in the form of partially degenerated areas resulting from cutting down of the blood-supply as the result of encroachment by the swollen and overgrown endothelial cells on the lumen of the vessels. Thrombi could not be found, in contradistinction to what had been described in botulism (Dickson [17], Semerak [18]). Evidences of inflammation were absent. Clinically also this case did not resemble botulism, but fitted in more with that group known as bacterial food poisoning, or what is popularly known as "ptomaine poisoning."

According to Rosenau [19], Savage [20] and Vaughan [21], there is no such entity as "ptomaine" poisoning. According to Dickson [17], food poisoning can be divided into three types:—

(1) Those produced by the ingestion of food substances which are inherently poisonous in themselves, e.g., ergot, mushrooms.

(2) Those produced by the ingestion of foods which are contaminated with bacilli of the *Paratyphoid enteritidis* group. These are called bacterial food infections.

(3) Those produced by the ingestion of foods which carry toxic products of bacterial growth. These are known as bacterial food intoxications and the only proved example is botulism.

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While the process was not absolutely limited to the cortex, it did not involve the vessels of the rest of the brain to anywhere near the degree it did those of the cortex. The ganglion cell changes were very different from those seen in the first case; shrinkage with tortuosity of the processes was common, and there was lipoid substance present in the cells, in contrast to its absence in the little girl. Lipoid was also more marked about the vessels.

When uræmia developed in this patient, it is probable that the same substances which affected the kidney also exerted its influence on the brain. This is more probable than the assumption that the original intoxication involved the kidneys first, and the retention which resulted produced the brain changes. We, therefore, feel that the adulterated foods were essentially responsible for the condition.

Summary and Conclusions.

(1) A case of food poisoning in a 7-year-old girl has been described. Marked gastro-intestinal symptoms with low fever, marked prostration and delirium formed the clinical picture. Pathologically the small vessels of the cortex were most involved. In them there was endothelial proliferation with mitosis and new vessel formation. Areas of partial softening were found, involving particularly the occipital and motor areas.

(2) In the second case the process was more prolonged and symptoms of uræmia developed prior to death. Here, too, tainted foods appeared to be the ætiological factor. Similar lesions were found in this case, but the process was more chronic, there being both progressive and retrogressive changes in the small vessels. Areas of incomplete softening were also found.

(3) Evidence of inflammation were absent in both cases.

(4) These cases fit in with the experimental work done on animals by metallic poisoning, and with the lesions described in the literature in severe intoxication with lead, manganese, carbon-monoxide and arsenic, and in certain severe infections.

(5) Both of these cases, while they resemble pathologically that found in syphilis, showed no clinical or laboratory evidences of that condition.

(6) Cerebral symptoms in severe, acute infections and intoxications may have their origin in vascular changes of this type with secondary cortical lesions. Both cases herein reported showed such symptoms.

In the bacterial-infection group the symptoms are characterized by the sudden onset of acute gastro-intestinal disturbances with relatively low fever and marked prostration. While the tendency is to recovery in a few days, in the more severe forms there is intense gastro-enteritis with collapse, and eventually death results. This type has practically always been due to spoiled foods of animal origin.

Botulism, or the food-intoxication group, on the other hand, results from foods that have been improperly preserved or canned. It is characterized clinically by the absence of acute gastro-intestinal disturbances and of fever. There are disturbances of vision with diplopia and ptosis; marked weakness of the skeletal muscles is a feature, with persistent constipation. The characteristic clinical picture is that of a severe intoxication and not of infection.

The relation of the changes found in the small cortical vessels to the clinical picture is important. It is well known that in all severe infections and intoxications, confusion, delirium and motor irritative phenomena may be present. It is also well known that in many of these cases mild changes of the vessel walls, in the form of swelling of the lining cells, have been found. It might be well to consider the effect of this vascular change rather than interpret the mental picture as dependent entirely on a primary change in the ganglion cells. May it not be that the ganglion cell pictures are due to cutting down of the blood-supply? In this brain, as in similar cases in the literature due to other types of toxins, the thickening of the pia-arachnoid occurred with the presence of cells that are phagocytic and is probably reactive in nature. The age of this patient at death, 7 years, made it an admirable case in which the vascular lesions could be studied without having to discount changes that are ordinarily due to advancing years.

In Case 2 the changes of the brain were more advanced than in the first case. We believe that this man had a mild chronic nephritis prior to his illness, and that the ingestion of the adulterated whiskey and ice-cream played a definite rôle, followed by the eating of meat that was probably contaminated, for both produced in him evidence of gastro-intestinal irritation and were the starting points for the severe toxæmia that affected not only the brain but the kidneys as well, and produced a picture of uræmia shortly before death.

Syphilis may be excluded as all the laboratory tests, including blood and spinal fluid, were negative. The absence of changes in the aorta is to be emphasized. Chemistry of the process was shown by regressive changes in the vessel walls, as well as progressive ones, resulting in shrinkage of the endothelial cells and occurrence of lipoid substances within the cytoplasm.

DISCUSSION.

Dr. R. M. STEWART said he was interested to note that one patient had acute nephritis, whereas the other escaped, though each presented a similar picture. Though the blood and cerebro-spinal fluid were negative to the Wassermann test, possibly syphilis might be responsible for the miliary foci of softening, which could merge in the lesions described in the brain. He thought that in some respects the picture was suggestive of mild syphilitic infection of the cortex. He congratulated Dr. Winkelman on the pictures shown, backed by very accurate description of the blood-vessels.

Dr. GORDON HOLMES was struck by the similarity of the lesions described in these two cases with those in the brains of two men who died with symptoms of acute poisoning, which he was able to examine. An unexploded shell rolled into a dug-out occupied by several soldiers and there underwent slow combustion. Some of the men were dead when removed, others unconscious, but in some the effects seemed to be only temporary. Some days later two of the latter group developed severe headache, became drowsy and then passed into a state of acute delirium in which they died.

The brain of one of these, and of a man who was unconscious from the first, was examined. The pathological changes were most pronounced in the cortex, but similar lesions of less degree were found in the basal ganglia. Vascular affections, almost identical with those described by Drs. Winkelman and Eckel in their more acute case, were the main changes, but there was also extensive softening of the fourth and fifth layers of the cortex, which was in places continuous over extensive areas, but in other places patchy.

These lesions were obviously due to a poisonous gas emitted from the slowly burning explosive; it was most probably carbon monoxide, but this could not be determined with certainty.

Dr. J. L. ECKEL: Replying to the question regarding the possibility of these cases having been due to syphilis, said there was no clinical evidence of that disease in either case, and further, the laboratory tests in both blood and spinal fluid were definitely negative. Further, there were no changes in the aorta suggestive of that condition. As we remarked in our paper the arterial changes in the severe toxic states resemble those described by Nissl and Alzheimer as occurring in syphilis. Very little work has been done on the brain in severe infections.

I should like briefly to mention two other cases we are working on but have not yet finished. The first was a child, aged 20 months, who died during a severe attack of erysipelas; the cortical vessels showed this same productive endarteritis, but no areas of softening, due probably to the fact the process had not lasted very long.

In the second case, a man, aged 22, who died following a severe illness associated with marked toxæmia, a similar picture was seen.

The cases described by Dr. Holmes impressed me as probably the result of carbon monoxide poisoning.

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MENTAL DISSOCIATION: ITS RELATION TO CATATONIA AND THE MECHANISM OF NARCOLEPSY.

BY E. MILLER
(*London*).

THE recent investigations of Pavlov and his school, their application to human reactions by Krasnagorski, and the light that these researches throw upon narcolepsy and the phenomena of sleep, have been most interestingly correlated by W. J. Adie. It is Adie's paper in particular that made me think along the lines that I have outlined in this communication.

The advance in our knowledge has thrown some light upon obscure fields of neurology, but some of this light has, I believe, possibilities for the study of those strange disorders of behaviour that we meet frequently in the field of psychiatry. It is for this reason that I bring before you a case of disordered mental function which illustrates some of the wider implications of Pavlov's work, and helps to fill up that battle area which lies between neurology and psychology.

The case in question concerned a young married woman, aged 26, with one child. The patient came under my notice last December, and I have observed her very closely ever since and from many angles.

She came complaining of periodic attacks of disorientation, during which she was only vaguely aware of her surroundings and was quite incapable of carrying out voluntary movements and of making a decision. She merely had a disturbed judgment of her visual perceptions. On occasion these attacks would be associated with disturbed sensations down the left side of the body, leaving her, after the attack, with a weakness on the left side. Attacks of this order, and those of disorientation and disturbed perception, would on occasion be precipitated by an emotional mood. Laughter, weeping or deep annoyance would be followed almost immediately by a sense of extreme muscular weakness, owing to which she had to lie down for fear of "falling in a heap."

Disorientation always followed these collapses and would last from a few hours to a couple of days. Illusory experiences of Gulliverian type were a characteristic accompaniment of these states. But with these psychological disturbances I do not intend dealing here, as they are not relevant to the problem with which we are here concerned. There have been frequent occasions in the past when emotion produced a state of sleepiness, but these have become comparatively rare. In her childhood, however, emotion would produce

sleep almost immediately, so much so that her mother always warned her against laughing and crying.

The present illness, if we may mark it off from the rest of her life, started four years ago, after her father's death and three months before her marriage. It reached the maximum of severity immediately after the birth of her child. At that time she passed into a phase of profound stupor for several weeks, during which she was unable to move her limbs; they were in a state of rigidity, her head felt fixed in a slightly retracted attitude, and her eyes gazed steadily into a strange and scarcely recognizable external world in which objects were grotesquely exaggerated in size. Sometimes she would smile or grimace without apparent cause and without power of voluntary control. These attacks recur with equal severity on the anniversary, and when the child's life touches her in the same way as it did during the confinement.

Previous history.—In childhood she had frequent attacks of sleep following on emotion, and she was also subject to sleep-walking.

At the age of 14 she developed "nervous debility," she wasted, did strange things and was described at the time as "negative" and "mute." At school, although bright and of more than average intelligence, she was antisocial. Menstruation came on at 18 and has always been scanty. Her physique never developed a characteristic feminine contour; she even prided herself on her boyish physique.

Family history.—Her father was physically robust, but impulsive and highly strung, and given to violent fits of emotion followed by weeping. Her mother is very nervous; she had to leave her husband because of his temper and irregularities when the patient was aged 9. Two sisters and one brother are very well and mentally normally balanced.

All grandparents were apparently normal, and no nervous or mental disease exists amongst uncles and aunts.

Physical examination.—She is a rather frail young woman; her physique it not strikingly feminine and her breasts are poorly developed. There is no organic disease of her central nervous system. Heart and lungs are clear, and her blood and cerebro-spinal fluid are normal.

We are all more or less familiar with the catatonic stupor and catatonic rigidity of schizophrenia, and with the mutism and perseverated speech and movements also associated with this condition, but I believe it is rare to find such narcoleptic attacks as in this case. On the other hand, the state of muscular weakness and drowsiness following on emotion has not been sufficiently sought for in the minor psychoses, such as hysteria with dissociation. Since investigating this case and reading Adie's article on narcolepsy, I have been careful to examine a large number of hysterics and cases of anxiety hysteria from this point of view, and I believe I have found, without suggesting this symptom to the patient, and mainly by interviewing relatives, that in about one

in ten of them emotion brings on sleep, or some condition of mental dissociation with or without loss of consciousness. In one case a fit of violent anger produced a sleepy state from which the patient awoke with varying degrees of hysterical dissociation, as aphasia, and then a flaccid paraplegia; there was complete recovery in a few days from all these dissociative phenomena.

It is important at this point to deal with what I regard as allied conditions which call for correlation; I mean the relationship between normal sleep and hypnosis.

In the process of hypnosis the subject passes through a phase of catalepsy with rigidity and thence to one of complete relaxation. The first phase, neurologically considered, suggests a condition in which extra-pyramidal control is dominant owing to cortical inhibition. It is not so much that the idea of sleep is suggested to the patient, but rather the monotonous repetition of the stimulus used and the ocular fatigue induced by fixation produces cortical inhibition, not complete because the auditory sense channels remain patent. The hyper-excitability during the early stage seems to indicate a thalamic condition of over-sensitiveness, due to the inhibition already existing in the cortex freeing the thalamus from higher control. This will allow for the passage of those instinctual and emotional processes, which in the waking state are controlled and reintegrated for the higher purposes of adjustment achieved by the cortex. The suggestibility obtained is merely the result of this lack of cortical discrimination, which would otherwise render the statements of the experimenter untenable or inacceptable. The experimenter then uses the dissociated masses, that is, reflex conditioned patterns, and attempts to deal with them on the affective level which hypnosis allows him to reach. Where, as frequently happens, the subject passes into a normal sleep, the inhibition has spread to the whole cortex, that is, the molecular dissociation becomes massive and the cortex is now asleep.

I think there is not merely here an analogy between sleep thus obtained and Pavlov's experimental sleep, but actual identical neurological mechanisms. In fact, this appears to be so much the case that frequently after repeated hypnosis of a subject, the hypnotic state passes immediately into one of deep sleep as soon as the accustomed stimulus is presented. Granting the hypothesis of the French school, that hypnosis is the artificial inducement of an hysteria, it seems reasonable to suppose that in all states of mental dissociation, from hysterical paralysis to fugues, the same inhibitory mechanism is involved.

Suggestion may therefore be regarded neurologically as the suppression of conditioned reflexes by the throwing in of another stimulus while the patient is, as it were, a "thalamic preparation," in the same way as in Krasnagorski's experiment the stimulation of the "active points" on the skin no longer produced salivation when the metronome was sounded.

If this explanation holds good, we have the nucleus of a theory of hysterical reaction formation from the molecular to the massive forms, and their resolution by hypnosis and by psychotherapy. In the latter event analytical procedure produces a reintegration of conditioned reflex patterns into the larger system of the biologically integrated personality.

If we turn back from these experimental considerations to the case cited above, we have here mechanisms involved which are closely allied to, if not actually identical with, those involved in the physiological sleep and inhibition of Pavlov's experiments and with the narcolepsy of Gelineau. The extrapyramidal rigidities, mutism and mimetic movements are processes of phylogenetically lower systems which appear when higher levels are somehow inhibited. Without expressly denying the integrity of the clinical entities produced by lesions, it is desirable in the interest of biological unity to treat these manifestations as one, for in this case they have appeared dynamically related in one and the same subject.

Observation of schizophrenes, particularly those who are passing into the catatonic state, forces one to see here a mechanism that is at one with that which produces the facies of post-encephalitic Parkinsonism. The rigidity is of the same order, and the grimaces which mark the face of a præcox are not absent from the face of post-encephalitic Parkinsonism.

It is a commonly observed feature of Parkinsonism that emotion will break down the facial rigidity, and sometimes excitement will suddenly bring an end to a state of mutism which has lasted for some time. In the catatonic schizophrene the same phenomena may be observed.

I do not believe that in all cases of schizophrenia, and particularly not in those with catatonia, is the rigidity controlled by volition, unless we assume, and we have no reason for assuming, the existence of unconscious volition. Forces outside the field of awareness must be regarded as neurological, and such activities, though they may be interpreted as symbolically infantile, are essentially due to the activity of the grey matter of the mid-brain which is no longer under cortical inhibition.

It was very difficult for me to distinguish at a short distance a case of post-encephalitic infantilism with rigidity from a case of true dementia præcox in the same mental ward. The distinction was obvious only when the former was asked to walk up the ward, which he did readily and with a complete absence of tremor of his left hand, stopping when told to do so, though not immediately. On the other hand, the præcox remained rigid and walked mechanically, with no apparent volitional power of stopping when commanded to do so. The latter, in other words, seemed to be less able to bring cortical control into action than did the former. Paradoxical kinesia and catatonic excitement must therefore be regarded neurologically as the same. In facial paralysis of cortical origin emotion may excite movements, and in Minkowski's decerebrate monkey movements were carried out without control of the cortical motor centres under the influence of emotion.

Observations on the similarity of catatonia and subcortical lesions have a long history. Kirscher, in 1646, obtained a cataleptic state with rigidity in hens by forcibly holding the wings and the head and making them fix upon a chalk line. Preyer later showed that restraint alone, without the fixation, was enough to produce the rigidity. Preyer believed this state to be affective in origin and produced the effect in all sorts of animals. Charcot obtained statuesque rigidity in men by stimuli arousing emotion suddenly. In 1874, Kahlbaum realized the neurological implications of the catatonic syndrome and called it a neurological phenomenon of spasmodic order—"Spannungsirresein." In 1924, Buscaino published his pathological findings in several cases of catatonic schizophrenia of ages ranging from 17 to 70. He found, especially in the extracortical areas, a large number of scattered lesions; those in the thalamus he regarded of particular importance, as they threw a light upon the dissociation in dementia præcox, particularly the schism between the intellectual and the affective life, the intrapsychic ataxia of Stransky.

The absence of pyramidal lesions and the presence of lesions in the extrapyramidal system, explained for Buscaino the abnormal muscular activities of dementia præcox. He associated the lesions of catatonia with the paleostriatum, catalepsia with the dentate nucleus, and stereotypy with lesions of the neostriatum. He believes that catatonia and post-encephalitic Parkinsonism are both due to the same toxic effects. While admitting the possibility of lesions in these areas in some cases, it is reasonable to hold, on a wider study of the behaviour of the schizophrene, that the reactions are not infrequently due to

profound disturbances of the mental life, using as their mechanism the nervous system and expressing themselves through a mid-brain system which is apparently prone to assume dominance under certain conditions of arrested development. In such cases it is not unreasonable to suppose that the condition arises as a disturbance of behaviour rather than as a result of pathological disorder of a gross kind, and that the objective neurological disturbances are the result of inhibitions set up in the mid-brain and thalamus, and that the latter, in view of its importance to the vegetative life and to the affective tone of the organism, is the seat of the mechanism of the emotional disturbances of dementia præcox and of the cataleptic states associated with it.

Adie says "that the thalamus very probably forms an important part of the nervous mechanism of sleep and of narcolepsy, but that its effects, if any, are produced, not by interference of ordinary sensory impulses but by a setting in motion of some inhibitory mechanism whose nature is unknown." The nature of inhibition remains unknown, but if we turn our attention from neurology to the vegetative affective life of the organism taken as a whole, the inhibitory forces are not as obscure as we might believe. The nervous system is only a mechanism which enables the organism to adjust itself to its environment; when this is relatively stable the regions below the cortex are sufficient, but under variable conditions which demand attention, discrimination and judgment of such variables, the cortex plays its part. Every such situation is a felt situation, events are met by a warmth which is derived from the whole organic working of the instinctive drives. If these are inhibited in their aims by conditioned reflex patterns, which only a complete history of the organisms will reveal to us, then other means of expression must be designed. If the organism is incapable of such adjustment which allows for harmonious working, then inhibitory mechanisms are set in action, and if these play upon a constitutionally weak machine, the pathological states of sleep, narcolepsy and dissociation are the result.

In the case which I have quoted all the phenomena involved in such an inhibitory process are present, from conditions similar at least to true narcolepsy to periods of mental dissociation. The mechanism that can explain these phenomena must be a nervous system that cannot stand up to difficult situations as an integrated whole, but the reasons for the inhibitory mechanism involved must be sought in the biological realm of behaviour.

DISCUSSION.

Dr. ADOLF MEYER said he had taken a great interest in this subject, particularly its catatonic aspect. He had tried to study man as an organism, as a personality who concerned the observer. It was a matter of satisfaction to see attempts made to understand the synthesis of that entity, which was done most adequately in terms of personality. The phenomena of sleep, and the phenomena which occurred in such an automatic way that one did not associate them with elaborate psychogenic developments, were of a neurological kind. He was sorry Dr. Percival Bailey was not present, as he had made some original observations on the correlation of lesions in the subthalamus with disorders of sleep.

Many attempts had been made to explain catatonia on the ground of complex extrapyramidal symptoms. Emphasis had been laid on the grey matter of the mid-brain, but the speaker felt somewhat confused when he thought of the great number of mechanisms at one's disposal for describing these phenomena. By exercising care in these matters we approached more and more a biological interpretation, and the view of man's life being divided into a waking and a sleeping life. So far, study had been devoted chiefly to the waking life; when the sleeping life has been further studied the nervous system would be found to be involved in it to a great extent.

STRUCTURAL CHANGES IN HUNTINGTON'S CHOREA.

BY THE LATE CHARLES B. DUNLAP,
Of the New York State Psychiatric Institute.

(PRESENTED IN ABSTRACT BY DR. ADOLF MEYER.)

THOSE responsible for preparing the programme of this meeting requested me to present to you the unfinished work on the striatum and cortex in Huntington's chorea of the late Dr. Charles B. Dunlap, Chief Associate in Neuropathology of the Psychiatric Institute of the New York State Hospitals. He was my pupil and associate from 1899 at the Worcester State Hospital, and my collaborator and friend throughout my connection with the Psychiatric Institute. Dunlap was no doubt one of the most critical and dependable students of brain structure. He succumbed to arteriosclerosis of the heart before he could bring to conclusion this study on the corpus striatum. It has nevertheless been made accessible in the best possible form through the editorial efforts of Dr. Bertram D. Lewin, for several years associated with him.

This study is based on seventeen brains of definite Huntington's chorea, and the brains of twelve other patients who had probably this disease, but with doubtful heredity, and on about thirty other brains with other, largely vascular, lesions of the striatum.

Dr. Dunlap recognized early the difficulty in obtaining in one section a complete picture of the striatum and of the relative sizes of its parts. Fig. 1 shows how in sections in different directions various appearances are obtained. It was only after reconstruction that he arrived at the estimate that in Huntington's chorea the striatum is less than one-half as large as in control cases, and that there is also a definite reduction of the cerebral cortex and its underlying fibre-masses (fig. 2), but no reduction in size of the thalamus, the brain-stem, or the cerebellum. In the striatum he determined a variable but definite and sometimes striking reduction of the number of cells and fibres of the putamen and caudate, and a corresponding shrinking of the ground-substance of the pallidum, leading to a slight crowding and apparent increase in the number of its cells in the sections. There was a slight diminution of

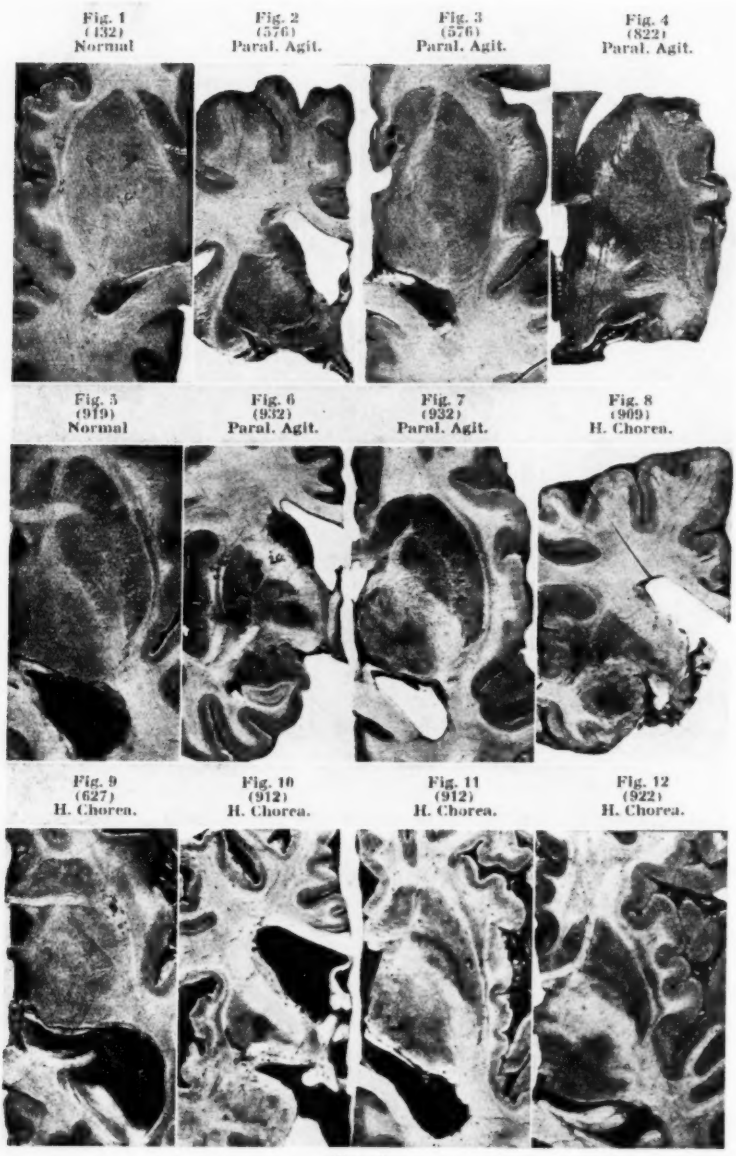
Fig. 1
(132)
Normal
Fig. 2
(576)
Paral. Agit.
Fig. 3
(576)
Paral. Agit.
Fig. 4
(822)
Paral. Agit.
Fig. 5
(919)
Normal
Fig. 6
(932)
Paral. Agit.
Fig. 7
(932)
Paral. Agit.
Fig. 8
(909)
H. Chorea.
Fig. 9
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H. Chorea.
Fig. 10
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Fig. 11
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Fig. 12
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H. Chorea.

FIG. 1.

FIG. 2.

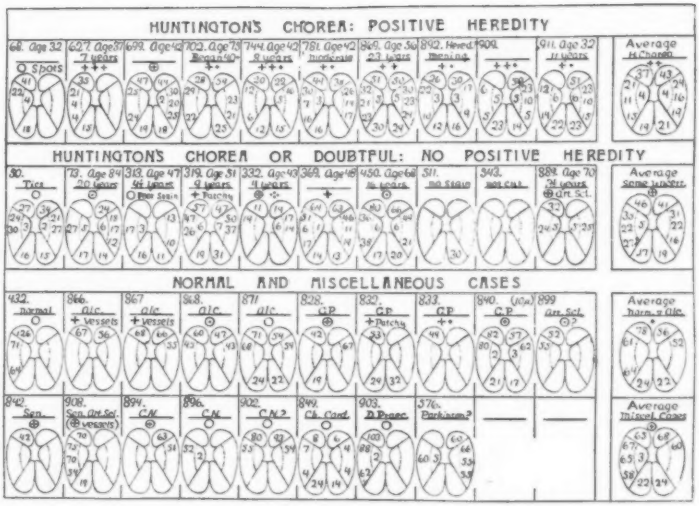
HUNTINGTON'S CHOREA: POSITIVE HEREDITY
HUNTINGTON'S CHOREA OR DOUBTFUL: NO POSITIVE HEREDITY
NORMAL AND MISCELLANEOUS CASES

FIG. 3.

the ansa lenticularis. He felt uncertain about the corpus Luysii, and has no data concerning the substantia nigra, but the red nucleus is described as not involved.

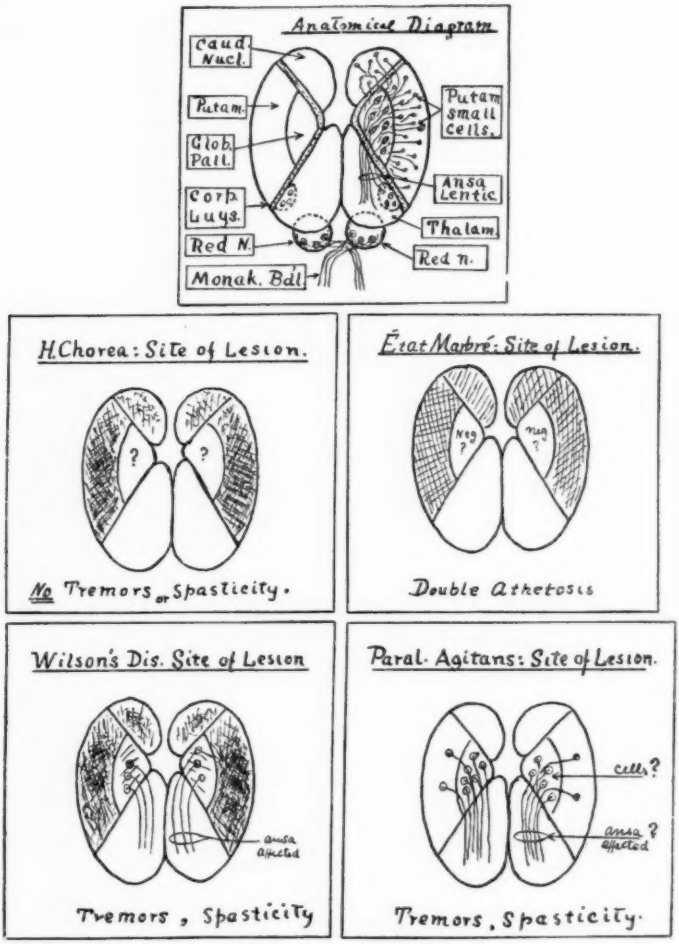

FIG. 4.

Dunlap puts his counts of cells and fibres in a summary way on diagrams, those of the striatum being best explained by figs. 3 and 4. He evidently found it impossible to give an adequate representation of

the fibre-masses of the internal capsule which might be used as a measure of the bulk of the cortex and white matter of the hemisphere. Fig. 4 gives a summary of his conclusions.

He had no case of Huntington's chorea in which there was not the characteristic loss of cells in the putamen and caudate, as well as reduction of the cortex and subcortical white matter. On these findings alone he was prepared to make a diagnosis, but he was unwilling to say that these accounted for the entire disorder and the clinical picture, or that there was any justification in localizing the origin of the motor disorders in the striatum alone.

He compared the lesions he found in the striatum in disorders with chorea and athetosis, with those in which the chief symptoms were tremor and spasticity :—

Huntington's chorea.—Reduction of the putamen and caudate without involvement of the pallidum, and without tremor and spasticity.

Double athetosis and "*état marbré.*"—Possible involvement of the pallidum in addition.

Wilson's group.—Tremor and spasticity, with disease of the putamen, caudate and pallidum.

Parkinson's disease.—Tremor and spasticity, with a doubtful reduction of cells of the pallidum, and atrophy of the ansa.

His cell-counts are exemplified in fig. 3, and leave no doubt of the diffuse reduction of cells in the putamen and caudate, and the slight apparent increase of cells in the pallidum, owing to reduction of its ground substance. The cell-counts of the cortex revealed no reduction in the number of cells, but most of them were somewhat shrunken, and the pencils or fans of radial fibres were reduced in size and number.

A neuroglial overgrowth in the striatum, with astrocytes with broad vascular feet, is represented in Dunlap's original illustrations.

Mere vascular lesions of the striatum, as Wilson has shown, fail to produce the so-called striatal symptoms.

With these data Dunlap gives a critical review of the literature. Only G. Kiesselbach gives actual cell-counts, and she also found marked atrophy of the basal ganglia, together with general atrophy of the central nervous system. The hemichoreas are regarded as too heterogeneous a group, since they have been associated with lesions of the superior cerebellar arm, with the presence of dural cysts, and disease in other parts of the brain, but in the majority at least the thalamus has been involved.

Dunlap warns definitely against the neglect of disturbances in other parts of the nervous system, and especially of the cerebral cortex and of the underlying fibre-masses, in the interpretation of these symptoms, and

remains true to the sound principle of pathology, that neither specific symptoms nor nosological entities should be hastily identified with one set of morbid lesions, no matter how conspicuous they may be.

The full paper, which will be printed in the *Archives of Neurology and Psychiatry*, furnishes in detail the technique, the material and the deductions underlying this concise summary.

A CASE OF SENILE CHOREA.

BY S. A. KINNIER WILSON

(London).

THIS article will be published in full with illustrations in an early number of *Brain*.

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HEMICHOREA RESULTING FROM A LOCAL LESION OF THE BRAIN. (THE SYNDROME OF THE BODY OF LUYS.)

BY JAMES PURDON MARTIN, M.D.

(*London*).

THIS subject arises from the case of a patient who came under my care at the Seamen's Hospital in February of this year. He was a man of large build, aged 62, formerly a seaman, and latterly employed as a night watchman on board ships in dock. He had had no previous illnesses, but at the time he came under observation had very atheromatous arteries, his systolic blood-pressure was 190 mm. Hg, and he had a considerably enlarged heart; the Wassermann reaction in his blood was positive.

Except for frequent headaches during the preceding six months, he had been well until February 8. On that morning, about 8 a.m., just after arriving home from his night's work, he felt giddy, staggered, and had a severe pain in the right side of his body. He sat down for a little, then felt better, had a meal and went to bed as usual. When he woke up at 4 o'clock in the afternoon he tried to take a cup of tea sitting up in bed, but his right hand "shook" so violently that he spilled most of the tea and he could not bring his cup to his mouth. Even when his wife held the cup he could not drink normally, but, as his wife described it, "he slopped the tea into his mouth and gulped it down." When he got up that evening to go to his ship his right arm was twitching and swinging about widely, and "he was throwing his right leg about," but, with some assistance from his wife, he managed to walk. When his wife saw him again, two hours later, the involuntary movements had become much worse, but in the morning he managed to walk home. His condition remained much the same for the next thirty-six hours, but on the evening of February 10 he became very agitated and unreasonable, turned on his wife as he had never done before in such a way that she was afraid of his violence; his involuntary movements were then worse than ever. The next day he remained in the same angry and uncontrollable mood, and in the evening made his way down to the ship. On the fourth morning after the onset of his illness he fell in his house and that day he was brought to hospital.

When I first saw him, and until his death fifteen days later, his condition was as follows: While he was awake his right arm and leg were unceasingly tossed about in a violent chorea. The movements occurred at all the joints of these limbs, but an unusually severe involvement of the shoulder and hip and elbow and knee gave them an amplitude not often seen in chorea. In form

they presented every combination of flexion, extension and rotation; they were quite irregular. They were free, quick movements, unhampered by any degree of spasticity. Their violence was such that the skin had been knocked off the knuckles and other parts of the affected hand, and also of the inner sides of both knees. The movements were continuous during the waking state, though they varied somewhat in intensity, being less when the patient was alone, and worse when he was called up to answer questions or perform test movements. With a great effort the patient could hold the right arm steady for about twenty seconds, every muscle of the limb being then taut in contraction. The right side of the head and face and the tongue were involved in the chorea, and to some degree the right side of the trunk. The patient usually lay with his head and eyes turned to the right, and he seemed to try to put the right hand under his head in order with his head to fasten it down on the bed and so restrain its movements. The movements of the face were less than was to be expected from the severity of the chorea in the limbs. In the early days of the illness articulation, though affected, was still distinct, but later it became greatly slurred. Swallowing was performed by spasmodic gulps. Breathing was always irregular, and was sometimes difficult owing to the irregular movements of the muscles of the throat, chest and abdomen. All these abnormal movements ceased entirely during sleep.

The patient's facial expression suggested great anxiety and restrained anger, and this seemed to be a true reflection of his mental state; during his stay in hospital he was at times irrational and uncontrollable, especially towards night; in the latter part he was at times disorientated, and often in a frenzy.

Associated with the movements was a moderate degree of sweating, almost confined to the affected side; the patient while awake always looked hot and the jactitated limbs felt warm and moist. The body temperature, as registered on the chart, remained steadily at 97° F. until a few hours before death. The temperatures of the two sides of the body were unfortunately not compared.

Further neurological examination revealed few other abnormalities. Voluntary power was normal in all the limbs; there was no sensory loss to pin-prick or light touch. At the first examination, but not subsequently, there seemed to be a slight hyperæsthesia of the choreic arm. The sense of position was normal, and pointing tests, including the Bárány tests, were accurately performed; pointing with the right hand was accompanied by choreic deviations of the moving limb, and the point indicated was touched by a finger, as it were, in flight. The appreciation of vibration was normal. The tendon-jerks were present in both arms and about equal on the two sides, those in the right arm being if anything less; the knee-jerk was definitely less on the affected (right) side than on the left; the ankle-jerks were approximately equal. The plantar responses were both definitely flexor throughout the illness. The abdominal reflexes were not obtained. The optic discs were normal, the pupils were approximately equal, but neither was quite

regular; both reacted to light, and as far as could be determined they reacted also to accommodation; the external ocular movements were full, but the eyes when at rest were usually deviated to the right. Except for the abnormal movements in the face, throat and tongue, the functions of the remaining cranial nerves were normal.

The patient died of broncho-pneumonia on the twentieth day from the onset of the chorea. He had been transferred to the National Hospital, Queen Square, ten days earlier, and a post-mortem examination was performed there by Dr. Greenfield twelve hours after death. The brain was hardened for a week in 10 per cent. formol saline before being cut. A point worthy of notice is that there was an abnormal formation of the arteries of the base of the brain; the basilar artery was formed by the right vertebral alone; at the upper end of the pons it curved again to the right, and behind the right mammillary body divided to form the posterior cerebrals, the left posterior cerebral artery being thus definitely longer than the right.

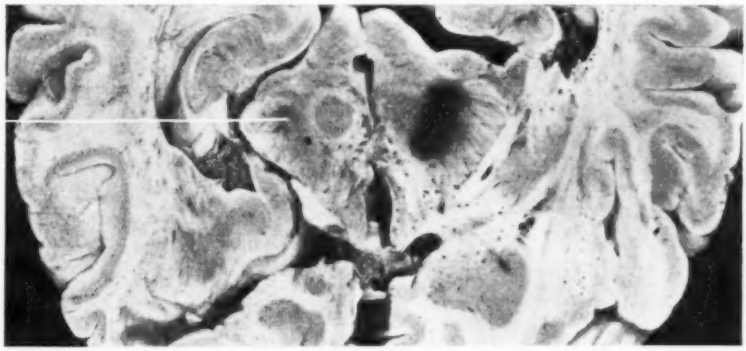

FIG. 1.—Horizontal section of the brain passing through the lower half of the hæmorrhage. The area of actual destruction is surrounded by a zone of staining. The right half of the brain is cut appreciably lower than the left and only a small portion of the right body of Luys is seen.

Section of the brain after hardening discovered a recent hæmorrhage destroying the corpus Luysii of the left side, i.e., of the opposite side of the body to the chorea. There were also some minor pathological findings in the brain. On the surface there was a general widening of the sulci, but especially of the right post-central sulcus. Within the brain there were many hæmorrhagic points, four of which—all old—amounted to lacunar softenings, 2 mm. in diameter; these were situated in the right thalamus, in the left ventral part of the pons close to the surface, and one in each dentate nucleus of the cerebellum.

The cerebral hemispheres were cut in Marie's *coupe d'élection* and then in horizontal slabs of 5 mm. in thickness above and below that section. The hæmorrhage appears in the two lowest slabs.

On the upper surface of the lowest slab (fig. 1) the cut passes on the left side through the upper half of the red nucleus and through the lesion well below (behind) its middle. The right side is cut appreciably lower, as is shown by the section of the optic tract, and only a small portion of the body of Luys of that side is seen. Within an area of staining the actual area of destruction can be seen, and its horizontal extent relative to the size of other structures can be judged. Its length at this level was almost exactly 1 cm. and its breadth approximately $\frac{1}{2}$ cm. On its medial side it was slightly concave and did not touch the red nucleus. On the lateral side, as was seen under the microscope, its ventral half was separated by the substantia nigra from the margin of the internal capsule, while more dorsally part of the capsule of Luys's body could be seen. A small dorsal fragment of the corpus Luysii was still present beyond the dorsal end of the hæmorrhage.

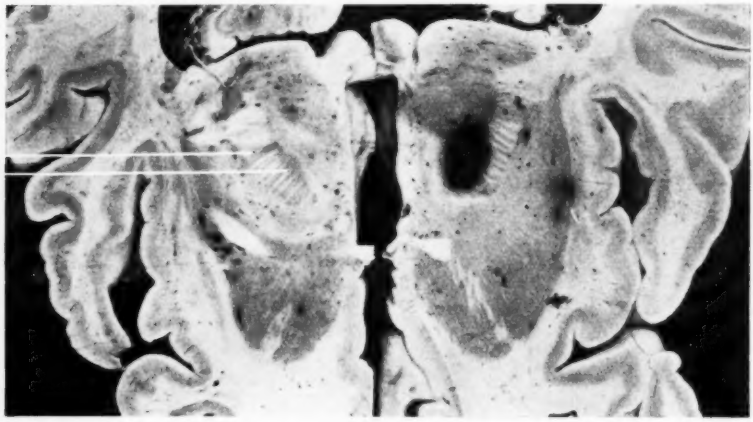

FIG. 2.—Horizontal section 5 mm. above that shown in fig. 1. The hæmorrhage is cut across near its upper limit. As in fig. 1 it is surrounded by a zone of staining.

On the upper surface of the slab immediately (5 mm.) above that just described, the hæmorrhage is (fig. 2) cut across near its upper limit. Its antero-posterior extent was less here than at the lower level, and the position of the damage as a whole was somewhat further from the middle line. Its length corresponded closely to that of the body of Luys. Medially, it reached to the zona incerta and laterally it bulged very slightly into the internal capsule.

For microscopic examination blocks from the horizontal slabs and from the cortex, mid-brain, medulla and cord were impregnated by the Marchi method, and those from the subthalamic region and mid-brain were cut in serial sections. From other blocks sections were prepared by Nissl's method, or by Loyez' method, or with hæmatoxylin and van Gieson's stain. The serial

investigation of the lower part of the mid-brain and of the pons and medulla by the Marchi method has not yet been completed.

The hæmorrhage was about the size of a pea and was approximately kidney-shaped, the concavity being in the lower half of the medial aspect. In all the horizontal sections on which the hæmorrhage appeared some small portion of the body of Luys was visible, and the vertical extent of the destruction therefore corresponded very precisely to the vertical extent of Luys's body, In nearly all the sections the fragment of the corpus Luysii which remained was its most dorsal portion (see fig. 3), and in some of the more caudal sections

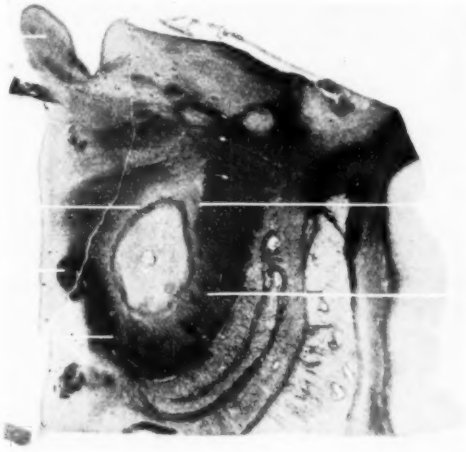

FIG. 3.—A section through the upper part of the hæmorrhage, stained by Loyez' method. It shows the lesion at its widest part where it bulged slightly into the internal capsule laterally and reached the zona inserta medially: its width at this level was 6·7 mm. Note the fragment of the body of Luys dorsal to the hæmorrhage.

there was a narrow lateral rim. Laterally, the hæmorrhage in its lower half was limited by the lateral border of Luys's body, but in its upper half it bulged slightly into the internal capsule, transgressing to a width of about 1·5 mm. at the widest part (fig. 3). Medially, in all the higher sections it reached to the zona incerta; in the lower sections it did not quite reach this structure. At no level did the destruction pass further medially than the zona incerta, and no other part of the thalamus was therefore involved in it, nor was the red nucleus injured by it at any level. Dorsally, the lesion, as seen in horizontal sections through its upper half, did not reach to the dorsal limit of the body of Luys and at no level did it exceed this limit. Ventrally, it seemed at nearly all levels to have just obliterated the bounds of Luys's body, but its ventral margin was wider than that of the corpus Luysii and consequently overlapped the position of the latter towards the medial side.

In short, the whole space destroyed by the hæmorrhage was almost exactly the position of the body of Luys and of that part of the lenticular bundle (H 2) of Forel which lies medial to it; the zona incerta was reached on the medial side and there was a slight bulging into the internal capsule laterally.

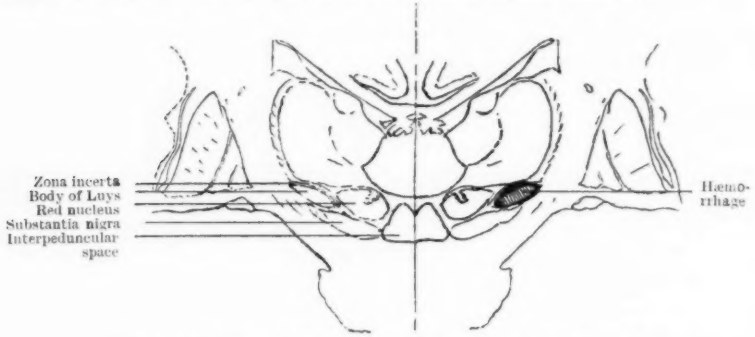

FIG. 4.—Diagram showing the vertical extent of the hæmorrhage.

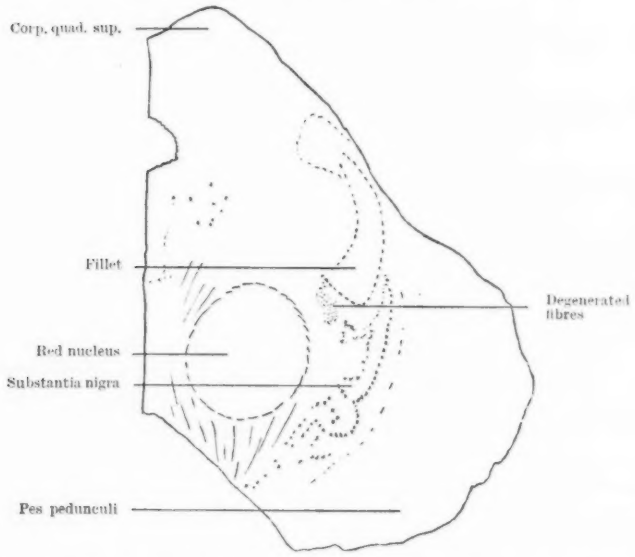

FIG. 5.—Outline drawing of a section through the upper part of the left half of the mid-brain, to show the position of the degenerated fibres.

In the Marchi sections secondarily degenerated fibres were well impregnated. In the mid-brain, beginning immediately caudal to the destroyed corpus, they formed a small but definite tract. It lay immediately behind the substantia

nigra, at first in the interval between the capsule of the lower part of the red nucleus and the medial edge of the fillet (fig. 5), then between the superior cerebellar peduncle and the edge of the fillet, and afterwards it became mingled with the medial fibres of the fillet. These fibres lay more laterally and more dorsally than v. Monakow's bundle. The fibres seemed to decrease in number as they passed down the mid-brain, but none of them were seen to enter contiguous structures or to decussate, and in any case it is probable that they lose their myelin sheaths before their termination. The examination is not yet complete and as some of my material is still uncut, I am not yet in a position to say whether they pass further caudally than the lower part of the mid-brain.

Above the level of the lesion nearly all the fibres passing across the internal capsule are intact, and are therefore descending fibres, but at the anterior end a few fibres, which appear to lie in the lenticular bundle (H 2) of Forel, have degenerated and can be seen passing across the internal capsule and obliquely upwards to enter the globus pallidus radially. Not many ascending fibres from any source seem to have been interrupted by the lesion. As the damage was limited medially by the zona incerta, it did not interfere with the fibres passing upwards from the red nucleus and superior cerebellar peduncle, since these lie medial to that structure; and, not extending dorsally beyond Luys's body, it avoided the fibres of the fillet.

A very few other degenerated fibres have been found passing from the focus of injury, one or two in the direction of Forel's subventricular decussation, and a few in the direction of the homolateral superior corpus quadrigeminum.

Cases Clinically Similar recorded in the Literature.

Cases of hemichorea attributable to local lesions of the brain demonstrated at autopsy are rather infrequent in the literature, and the difficulty of discovering them is greatly increased by the confusion of terminology. "Post-hemiplegic chorea" was the name given by Charcot to the condition afterwards called "athetosis," and cases published as hemichorea, especially in the older records, were often cases of athetosis or even of gross intention tremor. But of cases in which from the clinical description the movements had the freedom and spontaneity of chorea, as we now use that term, and the author's own description seldom leaves one in doubt, I have found about twenty with reports of post-mortem examination in the records of the last fifty years. In some of them the pathological descriptions are inadequate, but there are twelve which seem to be of scientific value. In chronological order they are as follows:—

Greiff, 1883 [8].—Female, aged 74, history of several slight strokes; sudden onset of left hemichorea; movements of large amplitude, psychic disturbances, hyperæsthesia and spontaneous pain of longer standing than the chorea and on same side; the patient died eight weeks after the onset of the chorea.

Post-mortem examination revealed four localized lesions in brain: (*a*) a hæmorrhagic slit in the middle of the right thalamus; (*b*) a similar slit caudal to the right thalamus destroying the body of Luys; (*c*) an old hæmorrhage in the right occipital lobe; (*d*) a small hæmorrhage in the centre of the left cerebellar hemisphere.

CANFIELD and PUTNAM, 1884 [5].—Male, aged 59. Slight right hemichorea for several weeks, then sudden exacerbation. Face little involved. Articulation affected. No sensory loss. Knee-jerk and ankle-jerk normal on right, absent on left. The patient could walk without assistance. Death in three weeks from the onset of severe chorea.

Post-mortem examination showed a hæmorrhagic softening the size of a large pea, "in the medial half of the left crus, opposite the posterior portion of the thalamus; it involved the substantia nigra and the pes beneath to a depth of 5 to 6 mm., and the tegmentum above almost to the nucleus ruber. The only ganglionic matter involved beside the substantia nigra was the so-called ganglion of Luys."

BONHOEFFER, 1897 [2]. Female, aged 55. Right hemichorea came on gradually and attained its full severity in the course of four weeks. Gross ataxia; no superficial sensory loss. A few isolated twitches occurred on the left side. The patient died from erysipelas about four weeks after the chorea had attained its full severity. Mental disturbances were present.

On post-mortem examination secondary carcinomatous deposits were found in the mid-brain, the largest exactly at the decussation of the superior cerebellar peduncles; another to the left of this involving the medial margin of the fillet, and a third, the size of a pin's head, on the right of the largest mass. The deposits lay entirely caudal to the red nuclei. The body of Luys and subthalamic region are not actually mentioned in the description, but it is stated that the thalamus was intact.

TOUCHE, 1901 [13].—Female, aged 70. Sudden onset of right hemichorea. Movements remarkable for their amplitude; face little affected. Articulation and swallowing involved. No sensory loss. Death from broncho-pneumonia a year after the onset of the chorea.

Post-mortem examination revealed two lesions in left side of brain, one in lateral part of the thalamus, the other destroying the body of Luys and the adjacent part of the internal capsule.

V. ECONOMO, 1910 [6].—Male, aged 71. Sudden onset of violent chorea of the left side twenty-four hours after a slight stroke causing some weakness of this side. Articulation affected. Transient right hemi-amblyopia. Mental disturbance. Death seven days after onset of chorea.

Post-mortem examination revealed a hæmorrhage the size of a cherry-stone lateral to the red nucleus, in the substantia nigra and in the tegmentum, involving the regio subthalamica and the corpus Luysii, and extending ventrally into the pes; it was separated from the thalamus by Forel's bundle H 2, except anteriorly, where it cut slightly into the ventral portion of the thalamus.

FISCHER, 1911 [7].—Female, aged 72. Sudden onset of left hemichorea with very large movements; face considerably affected. Articulation and swallowing disturbed. No mental disturbance. Death on the fourth day.

On post-mortem examination a hæmorrhage was found destroying right body of Luys "and only this." There was a superficial cortical defect on the orbital surfaces of both frontal lobes.

LEWANDOWSKY and STADELMANN, 1912 [10].—Male, aged 64. Right hemiplegia three years before; also slight left hemiplegia. Since onset of right hemiplegia slight right hemichorea; movements "not particularly strong, but still quite striking" (immerhin aber recht auffallend). Typical choreic character "without a trace of athetotic admixture." Face and head not involved. Right plantar reflex flexor.

Post-mortem examination showed on the left side of the brain an old hæmorrhagic softening along the lateral wall of the thalamus, destroying the lateral nuclei of the thalamus and involving the internal capsule. Ventromedially the lesion "extended somewhat into Forel's field." Serial sections were not done. The photograph of one section shows the lesion just touching the body of Luys at its lateral border.

BREMME, 1919 [3].—Female, aged 40. Right-sided chorea came on after removal of a carcinoma of the breast. Ataxia, and later superficial sensory loss on the right side and hemiplegia on the left. Hypotonia of the right side. Death three weeks after onset of chorea. Mental disturbances appeared a a few days before death.

Post-mortem examination revealed three metastases in the brain-stem: (*a*) One as large as a pea in the left body of Luys, involving also Forel's bundle (H2); the zona incerta was intact; (*b*) one as large as a walnut in right half of the pons and right cerebellar peduncle; (*c*) a smaller tumour in the pons, chiefly to the left of the middle line. There was also a small deposit in the extreme right of the right cerebellar hemisphere.

PETTE, 1922 [12].—Female, aged 69. Carcinoma of the breast three years before. Sudden onset of chorea of the whole of the left side. Death four weeks later.

Post-mortem examination showed a deposit the size of a pea in right regio-subthalamica, the body of Luys mostly destroyed (private communication to J. P. M.); red nucleus, thalamus, corpus striatum and cerebellar peduncles all intact.

CAMPORA, 1922 [4].—Female, aged 70. Abrupt onset of violent chorea in the left side. Face involved; articulation and swallowing affected. Pronounced hypotonia of affected side. Some psychic disturbance. Death after five weeks.

On post-mortem examination a small hæmorrhagic fissure was found in the right subthalamic region, 1 cm. in length, running transversely above the pes pedunculi. It destroyed most of the corpus Luysii, leaving only its most lateral part intact; medially, it extended into Forel's field and just touched the capsule of the red nucleus; laterally, it curved slightly round the extremity of

the locus niger; the internal capsule was not involved. "The lesion must have interrupted at least a great part of the ansa lenticularis." In Marchi sections there was "a conspicuous fibre degeneration external to the lesion, in the field where the ansa must pass"; also some degenerated fibres crossing to the nucleus lenticularis to enter the putamen.

JAKOB, 1923 [9].—Female, aged 75. The patient had had during the previous five years a series of "slight strokes" and transient aphasia, and conjugate deviation of the eyes to the left; no definite signs of paralysis in the limbs but some general diminution of power, particularly on the left side. Possibly some hyperæsthesia on left. Mental confusion.

On October 13, 1921, sudden onset of left hemichorea with large movements. Conjugate deviation of the eyes sometimes to right, sometimes to the left Condition remained unchanged for three weeks; then twenty-four hours before death the patient became comatose and the limbs of the left side were at rest and very flaccid. On the right side some spasticity. Death from broncho-pneumonia on November 3, 1921.

On post-mortem examination a recent hæmorrhage was seen, entirely destroying the body of Luys on the right side, and strictly confined to this ganglion, pushing Forel's bundles H 1 and H 2 upwards; sharply demarcated from the internal capsule and the substantia nigra. Medially, it extended beyond the bounds of Luys's body, but did not touch the red nucleus. Many hæmorrhagic points in the basal ganglia of both sides. Some small hæmorrhagic foci in the left internal capsule.

LLOYD and WINKELMAN, 1925 [11].—Male, aged 59. Old right-sided hemiplegia. Sudden onset of violent chorea on the left side. No trouble in chewing or swallowing; speech indistinct; mind at first clear but afterwards the patient became delirious. Death from broncho-pneumonia three weeks after the onset of the chorea.

Post-mortem examination revealed: (*a*) An old softening in the left internal capsule (corresponding to the old right hemiplegia); (*b*) a recent hæmorrhage which extended along the medial side of the putamen, passed by a narrow band across the internal capsule in its posterior part, "impinged on the corpus Luysii and extended into the pes pedunculi." There were small areas of softening in the thalamus on each side.

In these thirteen cases of hemichorea there were ten in which the body of Luys was completely, or almost completely, destroyed; in two others hæmorrhages "impinged upon" the body of Luys ventrolaterally and passed for a short distance caudal to it, thus probably interrupting the fibres which emerge caudalwards from its lateral aspect near its ventral extremity. In the remaining case the only lesions described lay at the level of the decussation of the superior cerebellar peduncles, and one of them interrupted the most medial fibres of the fillet and must have interrupted the descending tract which was found degenerated in my case. (See also Addendum, p. 649.)

Syndrome of the Body of Luys.

The cases of Canfield and Putnam, Economo, Fischer, Pette, Campora and Jakob, and my own case, in all of which the injury was almost confined to the corpus Luysii, enable us provisionally to attribute a group of symptoms to the destruction of this body and the consequent release or disturbance of the function of other structures. It is true that in my case Forel's bundle H 2 and the zona incerta were involved in the lesion as well as the body of Luys, but in the cases of Pette and Fischer, and probably in that of Canfield and Putnam, these structures escaped, and the only common injury in all the cases seems to be that of Luys's body. The same group of symptoms was present also in the cases of Greiff, Touche and Bremme, in which there were multiple lesions, one of which, in each case, destroyed Luys's body. The main elements of this group of symptoms are as follows :—

A violent chorea of the opposite side of the body, with unusual involvement of the shoulder and hip, and, therefore, with movements of unusual amplitude. The affection of the face, according to nearly all the descriptions, is less than one would expect from the amount of choreic movement in the limbs. Speech and swallowing and respiration are all involved in the chorea. The movements cease entirely during sleep.

The tendon-jerks of the affected side are usually less than those of the other, indicating a moderate degree of hypotonia.

In a number of cases it is recorded that the temperature of the choreic side was higher than that of the other half of the body, and in my case there was some unilateral sweating.

In nearly every case there has been a mental disturbance—at first chiefly an emotional change (excessive anxiety), and afterwards loss of memory, confusion and disorientation.

There are no signs of pyramidal disease, no loss of superficial sensation or of sense of position, no defects in the pointing tests.

In all the recorded cases in which the syndrome was fully developed death has resulted in a few weeks, the maximum duration of life recorded after a sudden onset of violent chorea being eight weeks (Greiff). But with less severe symptoms the period of survival may be very much longer.

In all the cases in which the mode of death can be ascertained, except Bonhoeffer's case in which death was due to erysipelas, the patients died of broncho-pneumonia. Touche's patient, who lived for a

year after the onset of the chorea, had three attacks of broncho-pneumonia during that time. It is remarkable that none of the patients died of cerebral hæmorrhage or of cardiac failure. I think that the tendency to broncho-pneumonia is possibly to be correlated with the respiratory disturbances of the chorea and to be included as part of the fully expressed syndrome.

Pathogenesis of the Chorea resulting from Localised Cerebral Lesions.

The cases which have been referred to give no indication of the structures which must be intact in order that chorea may occur, but it may be observed that in all the red nucleus was intact, the substantia nigra nearly so, and the pyramidal tract at least competent. It is likely that the relative integrity of all these structures is to be correlated with the conditions of tonus essential for the occurrence of a true chorea, but we have not sufficient knowledge to understand whether it is related to the choreic movements.

In describing the secondary degeneration in my own case I drew attention to two descending groups of fibres—a lenticulo-Luysian, and a Luysian-mesencephalic. We may describe these as forming a descending system.

Of the thirteen cases of chorea which I have considered, the body of Luys was actually destroyed in ten; in one other there was a lesion definitely in the fibre-path which seemed to descend from it. Of the remaining two cases, the lesions in both "impinged upon" the body of Luys ventro-laterally, that is, at the part where its descending fibres emerge, and may have interrupted these fibres. In all the cases the lower part of the system seems to have been interrupted.

There is no valid evidence that a focal injury of the upper part of the system causes chorea, and in fact much clinical and pathological evidence and Wilson's experimental work are against any such supposition. The fact that symptoms occur when the interruption is at or below the main station of the system is further evidence that the system is physiologically a descending one, and affords the suggestion that the impulses which bring about the choreic movements arise at an anatomically and physiologically lower level.

Wherever they arise and whatever structures must be intact in order that they may occur, the primary control of these impulses seems to be vested in the body of Luys; as long as that primary control is intact

chorea from a focal injury does not seem to occur. The anatomical connections suggest that there is a higher control represented in certain cells widespread in the striatum and pallidum, and it may be that from these nuclei the function of the body of Luys and its underlings is directed in relation with other cerebral functions.

Addendum.

Through the kindness of Professor Vincenzo Bianchi, I am now able to refer to two other cases of chorea of which no adequate description was available at the time the foregoing paper was read. They are cases described by the late Professor Leonardo Bianchi, one in 1885, the second in 1909 [1]. In the former case there was a left hemichorea of several years standing in a lad aged 18; after death a tubercle was found occupying the right subthalamic region ventrolateral to the red nucleus, and extending caudally throughout the length of the right cerebral peduncle in the lateral part of the tegmentum. The body of Luys was included in the destruction.

In the second case a chorea of the right side had come on in a young woman, aged 20, and several months later similar movements had appeared in the left side also; these symptoms persisted unchanged until the patient's death ten years later. In the left half of the brain there were found several foci of sclerosis, one of which occupied the subthalamic region and had destroyed the body of Luys. In the right half of the brain the cerebral hemisphere was normal and the only lesion was in the mid-brain; this was "a patch of sclerosis which occupied the most ventral portion of the tegmentum and extended for its greater part into the section of the pes in front of and ventral to the mesial fillet, which latter was also involved, together with a portion of the substantia nigra and the stratum intermedium." The figure shows that the involvement of the fillet was in its medial portion. The superior cerebellar peduncles were intact.

The case of left hemichorea and the case of Bonhoeffer are the only recorded instances in which the lesions on the opposite side of the brain were confined to the mid-brain. In the two instances the lesions are in divergent situations, and all that they have in common is the interruption of the most medial portion of the fillet. This common element is a small one, and the fact is significant that it includes the site of the small bundle of fibres which was found degenerated in my case. It goes to support the view that a chorea results either from destruction of the body of Luys itself or from interruption of the fibres which descend from it.

My thanks are due to Dr. Greenfield for his help and advice in regard to the pathological examination and for the preparation of the photographs; to Dr. Pette, of Hamburg, for his kindness in sending me information in regard to his case of chorea, and to Professor Vincenzo Bianchi for sending me the report of his father's cases.

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Discussion on the Papers by Drs. Dunlap, Wilson and Martin.

Dr. Adolph Meyer pointed out the importance of Dunlap's work in a consideration of the pathogenesis of hemichorea. It is almost impossible to come to any conclusions from the hitherto recorded cases associated with local lesions, since in some the disease involved the corpus striatum, in others the cerebellar peduncles, and the condition has even been described where the only lesion was a subdural cyst over the cortex. It is possible, as Dr. Wilson has suggested, that the dropping out of a part of the efferent system of the striatal mechanism may produce a condition in which activity of other portions of the brain causes the symptoms of hemichorea.

Dr. Weisenburg agreed with Dr. Kinnier Wilson that a positive function cannot be ascribed to dead cells, and that there was an unjustifiable tendency to attribute too many symptoms to disease of the striate body. He was interested to learn of the case in which the tremor and athetosis ceased after the post-central convolution had been excised. In a case of bilateral athetosis, Dr. Frazier, of Philadelphia, removed the arm centres on both sides; for a few days the athetotic movements ceased, but they then returned, and in a short time were as severe as ever.

Dr. Brouwer said that last year a lady, aged 60, was brought to him with typical chronic chorea, the movements having started five years previously. Other members of the family suffered with similar movements. She had had an acute endocarditis at the age of 5 years, and rheumatism when 7 years old. She had also arthritis of several joints. She died some weeks later. On *post-mortem examination* chronic and

acute endocarditis was found. The brain was studied in serial sections; the nucleus caudatus was atrophied, but the globus pallidus was unaffected. There were many changes in the cortex, especially in the frontal lobes, and an atrophy of the corpus callosum. It is of interest that the symptoms of Huntington's chorea were associated with a rheumatic history and endocarditis, even though there was a family history of the disease. The case will be published in full later.

Dr. S. A. KINNIER WILSON pointed out that in the group of cases collected by Dr. Martin the lesions were destructive and therefore left unsolved the problem of how the choreic symptoms arose. Dr. Martin's own case is important owing to the small size of the lesion, but he thought one should be chary of ascribing it all to the symptoms which the patient presented. Possibly these were due to the interruption of an ascending system, whereby the descending cortico-spinal system was set free.

Dr. MARTIN, in reply, said that if there had been more time to give to the paper he would have referred to some of the structures that were intact in his case and in the other cases he had described. He had never for a moment lost sight of the fact that the choreic movements must arise from surviving structures; he had not made the mistake of ascribing positive symptoms to a destructive lesion. Dr. Kinnier Wilson thought that he interpreted Bonhoeffer's case wrongly, but he felt sure Bonhoeffer had not interpreted it rightly, because he attributed the occurrence of the chorea to the lesion, which interrupted both superior cerebellar peduncles, and yet the chorea was almost entirely, unilateral. Dr. Martin did not think the chorea could be accounted for by the lesion of the superior cerebellar peduncles.

THE ANATOMICAL IDENTITY OF THE WERDNIG-HOFFMANN AND OPPENHEIM FORMS OF INFANTILE MUSCULAR ATROPHY.

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AND

RUBY O. STERN, M.B., B.S.

THE similarity of the anatomical picture in the disease which Oppenheim called "myatonia congenita" to that in the form of infantile paralysis which Werdnig and Hoffmann had previously described, is not by any means a new observation; it has been made by many. In 1909, Rothmann, on the basis of the few post-mortems that had been made up to that date, considered that it was impossible to distinguish between these diseases by the morbid anatomy, since both were due to atrophy of the lower motor neuron. But he suggested that a differentiation might be made either by considering the congenital cases as Oppenheim's disease, and those which occurred later as of the Werdnig-Hoffmann type, or by classing those which improved under Oppenheim's and those which got worse progressively and died under Werdnig-Hoffmann's form. We shall show from the histories of the published cases how impossible it is to make any such distinction.

Wimmer had even earlier, in 1907, suggested that the diseases were clinically inseparable. Slauck, a pupil of Hoffmann's, writing in 1921, referred to some notes which his late master had been making on the subject at the time of his death, in which the words occurred: "Myatonia is not a special form of progressive spinal muscular atrophy, but is the disease itself."

It would be difficult to add anything to the discussion on the nature of the diseases given by Slauck, who has combined the gleanings from Hoffmann's clinical and critical notes with his own pathological observations in two fresh cases. But several reasons have made it seem worth while to us to revert to the question of the identity or distinction of the anatomical picture in the two diseases. In the first place, Slauck's paper, coming from a pupil of Hoffmann's, bears the mark of partisanship, and therefore has not perhaps received the attention which

it deserves. Secondly, in Anglo-American and in German literature, at any rate, the name "amyotonia" or "myatonia" is often used to describe cases which on clinical grounds might more correctly be described as Werdnig-Hoffmann's disease, and vice versa. This is easily understood if, as we consider, the diseases are identical, but while tradition and teaching continue to separate them it leads to endless confusion. In the third place, we have the opportunity of presenting the anatomical examination of four cases, three of which were diagnosed as amyotonia and one as Werdnig-Hoffmann paralysis. One of the cases of amyotonia was familial and congenital and survived to the age of 13 years.

Definitions of the Two Diseases.

One of the most recent as well as the best definitions of the Werdnig-Hoffmann form of infantile paralysis is that given by Collier and Adie in Price's "Textbook of Medicine." They define it as: "A malady of the first year of infancy, often incident upon several children of the same parents and characterized by the gradual development of progressive muscular weakness and atrophy which affects the proximal muscles first and most, increasing to a complete paralysis of trunk and limbs and finally affecting the bulbar muscles. The disease is invariably fatal in from a few weeks to several months. The most striking pathological changes are a progressive degeneration and disappearance of the ventral horn cells of the spinal cord and of their analogues in the brain-stem." They state that the disease may be pre-natal in onset, but distinguish it from amyotonia congenita by the tendency to improvement and by the presence of contractures in the latter disease. The only criticism we can make of this definition is that in several of the reported cases death has been delayed until the age of 3, and in some classical examples, such as those of Thomson and Bruce and of Hoffmann, the age of 6 years has been reached.

Oppenheim in 1908 described the disease which he called myatonia congenita as one in which "there is a striking flaccidity of the muscles of the lower, sometimes also of the upper limbs, much less often those of the trunk. The limbs may be moved like loose appendages. The tendon reflexes are weakened or lost. The muscles are not visibly wasted, but the electrical excitability is more or less diminished, or may even be absent. Active movements are feeble, the child appears paralysed, yet on close examination one recognizes that in most cases a certain amount of power of movement is present. . . . I have established that this condition is capable of gradual improvement."

As amplification of this definition, Collier and Wilson in their article on amyotonia congenita say, "We are bound upon the present evidence to emphasize a post-natal as well as a pre-natal onset for Oppenheim's disease."

If, therefore, we attempt, taking Rothmann's first suggestion, to separate such cases into two groups, according as they are congenital or not, we are faced with many difficulties. Not the least among these are the familial cases reported by Beevor, Bibergeil, Popper, Aikman, Slauck, and others, in which one child was affected at birth and other children of the family at varying stages of infantile life. Bibergeil's family is of special interest, as his first little patient was well and strong up to eight months of age, and could actually stand at that age, thereafter becoming weak with muscular wasting and fibrillation of the tongue. A younger child, a twin, never moved properly from birth, its weakness contrasting with its twin's strength; but it could still, at the age of 3 years, move almost every muscle weakly. The first child was thus a typical example of Werdnig-Hoffmann paralysis, and the second an equally typical case of Oppenheim's disease.

If, on the other hand, we attempt to classify these cases by the other method, regarding the cases that improve as Oppenheim's disease and those in which the weakness progresses steadily as Werdnig-Hoffman paralysis, we have two difficulties. First, we shall not find many records of post-mortem examinations on cases of Oppenheim's disease, although the case of Collier and Holmes belongs to this category. Secondly, we have other families in which cases of both kinds occurred (Knox and Powers, Pearce). Pearce observed a pair of twins, both of whom were weak at birth, but whereas one became progressively stronger, the other went steadily downhill.

In the table we have drawn up we have included all the cases with post-mortem reports in which the diagnosis of Oppenheim's disease could reasonably be made. We have collected in it all the congenital cases, and also those cases in which, although the disease made its appearance shortly after birth, the symptomatology was considered by the authors to resemble more closely Oppenheim's disease than Werdnig-Hoffman paralysis.

Although we do not wish here to enter at any length into the clinical side of the question, we should like to refer briefly to the similarity which the two diseases present in many clinical points. First, as to the course of the disease; in a large number of cases of both types, even in such classical examples of Werdnig-Hoffmann paralysis as the case

reported by Thomson and Bruce in 1893, there have been periods of standstill, and even of amelioration in the paralytic symptoms. This is illustrated also by our Case 3, in which a slight improvement was noted after the child had been under observation for seven months. Even when there seems to be a steady progress in the degree of muscular weakness, the paralysis of certain muscle-groups may undergo remission. Thus, while the musculature of the chest and back is becoming weaker a certain degree of power may return in the hands or feet, or a weakness of the facial muscles, such as was observed in our Case 4, may disappear. This may be due in part, or even entirely, to the commonly observed fact that a child as it grows older will learn to use a partially paralysed muscle, or to make better use of those muscles or portions of muscles which remain intact. Certainly it has never been shown anatomically to be correlated with evidence of repair of the neuro-muscular mechanism. In the cases collected by Hoffmann, some of which were followed for many years, the remissions were never permanent, and almost always, sooner or later, the weakness began again slowly to increase. One patient was examined by him at the age of 21, and then "presented such a picture of misery as he had never before observed in his long practice."

The second point is the constant sparing of the diaphragm in both diseases. We have not encountered a single case in which death occurred from diaphragmatic paralysis, whereas death from intercostal paralysis and its pulmonary complications is the rule. This is the more remarkable, since in some cases there appears to be, from a very early stage in the disease, an almost complete atony or paralysis of the musculature of the neck.

The third point is one of rarer occurrence, viz., weakness of the muscles supplied by the cranial nerves. Of these, only the facial and tongue muscles have ever been definitely observed to be affected. Although in some instances the voice has become weak, this is probably due more to the child's general weakness and intercostal paralysis than to affection of the laryngeal musculature. Thus in Thomson and Bruce's case it was noted that an improvement in general health was associated with a louder voice. The difficulty in swallowing, which has been reported in several cases, also appears to have been due to paralysis of the tongue and facial muscles. Affection of the eye muscles has never been observed. This weakness of the facial and tongue muscles has been claimed by some as evidence of amyotonia congenita, and by others as occurring typically in Werdnig-Hoffmann paralysis. Hoffmann laid

emphasis on paralysis of the tongue in his disease, as changes in the electrical reactions could be more conveniently studied in it than in the well-covered muscles of the trunk and limbs. Although Reuben considers that the tongue is more often affected in amyotonia, it is certainly often also paralysed in cases which start during the latter months of the first year of life, as in Bibergeil's case. But it seems as though it were a symptom which is apt to develop late in the disease, and when rapidly increasing weakness leads to death at an early age it is not so likely to be observed.

In our cases certainly it was a late symptom, and the large number of acutely chromatolytic nerve cells which we found in the hypoglossal nucleus in three of our cases, taken along with the relatively slight changes in the musculature of the tongue in those cases, suggested to us that the disease process had reached the bulbar nuclei only a short time before death.

There remain many points of supposed difference between the clinical pictures of the two diseases. Of these perhaps the most important is the familial nature of Werdnig-Hoffmann paralysis contrasted with the non-familial character of Oppenheim's amyotonia. This distinction, which was emphasized by Collier and Wilson, falls to the ground if we include all congenital cases as amyotonia, and it is difficult to accept in view of such instances as Pearce's pair of twins, to which reference has already been made, and other familial congenital cases which improved steadily from birth (Foot, Knox and Powers). Krabbe considered that the congenital cases might be separated into two types, one, "a congenital familial *progressive* spinal muscular atrophy, a type which is most related to Werdnig-Hoffmann's type," the other, or true amyotonia type, "consists of a congenital hypotonia, hyperflexibility and weakness, but no atrophies. If the patient does not die from intercurrent diseases it may be assumed that he is cured." It is the object of our paper to show that even the latter type, when the patients "die of intercurrent diseases," is associated with the same anatomical changes in the spinal cord as are both the congenital and later cases of the Werdnig-Hoffmann class. In fact, Krabbe appears to have excluded from this second group of "true amyotonia" many cases in which clinical improvement was observed by the authors (Collier and Holmes, Griffiths and Spiller, Archangelsky and Abrikosoff), simply on the grounds that the post-mortem findings in these cases resembled closely those of the Werdnig-Hoffmann type. He also excludes Rothmann's case, although in it the diagnosis of amyotonia was made in Oppenheim's clinic.

Pathological Anatomy.

In reading over the reports of the post-mortem examination of cases of Werdnig-Hoffmann paralysis, and of amyotonia congenita, we are struck by the constancy of the pathological picture. If we appear to pay little attention to the post-mortem reports in cases diagnosed as Werdnig-Hoffmann paralysis, it is because in them the descriptions are so similar as to be almost stereotyped. Nor is any divergence found between the classical textbook description of the morbid anatomy of the disease and the description of individual cases. Certain minor differences are undoubtedly found between different cases, sometimes due to the varying duration of the disease, and sometimes to differences in interpretation. To these we shall refer later. But the main points are constant. These are: (1) Atrophy and degeneration of anterior horn cells in the cord; (2) thinness and poor myelination of anterior roots; (3) slenderness and deficient myelination of the peripheral nerves with, in most cases, a large proportion of very thin myelin sheaths; (4) atrophic changes in the muscles.

A glance at the table in which we have summarized the twenty-eight cases of amyotonia congenita, of which there are post-mortem records, shows that in all except three the same pathological picture is found. In some cases no mention has been made of the anterior roots or peripheral nerves, and a few authors have stated the condition of the peripheral nerves examined to have been normal. But in all twenty-five cases there has been at least a diminution in the size and number of the anterior horn cells in the cord, and atrophic changes in the muscles.

Before entering on a fuller discussion of these pathological changes it is necessary to examine very closely the three cases in which no changes in the central nervous system were found, i.e., those of Spiller, of Lereboullet and Baudouin, and of Councilman and Dunn. Of these Spiller's is perhaps the most important, as Oppenheim accepted it, "although a somewhat doubtful case," as confirming his supposition that his disease was due to a delayed development of muscles, the nervous system being intact. In Spiller's case the first symptom, noticed at the age of *five months*, was that the child did not seem to take notice of things as he should. The only symptom referable to the muscular system on which the parents volunteered information was that he had never held things in his hands. When examined at 20 months of age the right optic disc was noted by De Schweinitz to be atrophic or pallid (?) without any choroidal change. Spiller, however, thought

the discs normal. The child had a convergent squint. The limbs were extremely atonic but could be moved voluntarily at all joints although weakly. However, when pricked with a pin the limbs were drawn away "with considerable force." The child had never been able to stand. He could sit when balanced, but his head fell slightly forwards. Although he took the breast well at home he could not be induced to take food in hospital and was always fed with a nasal tube. He died at the age of 23 months. A fairly full examination was made of the central and peripheral nervous systems without the discovery of any abnormality. The only changes were in the muscles, which are described as being small, pale, and hyaloid in appearance. Microscopically only small muscle fibres could be seen. There was considerable excess of interstitial connective tissue and fat in the muscles from the sole of the foot, but not in the other muscles examined.

This is an anomalous case. There was certainly atony of muscles without much weakness, but there was also apparently mental retardation or deterioration, as evidenced by the failure to notice things, or to swallow from a spoon or bottle although he could take the breast. The statement that the voluntary movements were weak is counterbalanced by the observation that movements in response to painful stimuli were performed "with considerable strength," giving the impression that the latter were definitely stronger than the former. If this was so it would seem to indicate that the weakness of movements was not due to any lesion in the muscles, and we should have to refer it to some undiscovered lesion in the cerebellum or cerebrum. The only microscopic abnormality found, that in the muscles, differs both from the condition in myopathy and from that in Werdnig-Hoffmann paralysis. The muscle fibres are described as all small in size, but no measurements were given. The child only weighed 14 lb. at 23 months, and it seems possible that the small size of the fibres may be referred rather to the general malnutrition of the child and the absence of normal muscular activity than to any disease in the muscles themselves.

The case of Lereboullet and Baudouin also appears to be doubtful. The child was subject to fits, during which the muscular atony disappeared; and on the day before his death a condition of hypertonicity of the limbs and cyanosis of the face replaced the hypotonia and waxy pallor which had been noticed when he was first examined. The reflexes from being absent became exaggerated and internal strabismus appeared. This condition persisted until death. The authors considered that the onset of hypertonia only proved "that a spasmogenic

excitation can triumph over the myatonia." The criticism which we have made on Spiller's case may be equally directed against this one. It appears to us impossible that a hypotonia, associated with complete paralysis of most of the muscles of the body, and due to disease of the muscles, should suddenly disappear and be replaced by hypertonia and contracture. That this should have occurred is to us evidence that the cause of the hypotonia was situated more centrally than the peripheral motor neuron.

The case reported by Councilman and Dunn does not admit, however, of any criticism from a clinical standpoint; nor is it easy to see how in the very complete examination which the authors made of the central nervous system any disease could have been overlooked. The description which they gave of the muscles tallies exactly with that of all other cases of amyotonia, and they add that there was degeneration of the smaller nerve bundles in the muscles and absence of fine nerve filaments going to the atrophied muscle-fibres. It is possible that their negative findings in the central nervous system may have been due to error of interpretation; that they expected to find more evidence of recent disease than is usually present in amyotonia and that a comparative count of anterior horn cells in this case and in a normal child of the same age would have revealed a greater departure from the normal than was at first sight obvious.

Discussion of Pathological Changes.

(1) *Atrophy and degeneration of anterior horn cells.*—In all the twenty-five other cases atrophy and degeneration of anterior horn cells was described. In most of them the diminution in number is considerable and is usually described as very great, but in Batten's second post-mortem case (his Case 5, H. C.) there was little loss in number of cells, although there was some chromatolysis of the cells and Marchi degeneration in the ventral roots. It is important that in all the case records, in which special reference was made to this point, there was a larger number than normal of small nerve cells in the ventral horns. It seems, therefore, as though a certain number of the large cells had either undergone atrophy or had never fully developed. But evidence of degeneration of large cells is afforded, both by definite chromatolytic changes in some of the cells, and by the presence of what Hoffmann described as "empty beds," the basket work of myelinated fibres round the large nerve cells having persisted though the cells have disappeared

(fig. 1). Brouwer has described this appearance in amyotonia congenita. He says: "In Weigert-Pal preparations one can see the places where the various cell-groups should lie; only the cells are absent." Kaumheimer also found a similar condition in the hypoglossal nucleus of his case, and noted that the cell-beds became filled up with neuroglial nuclei and fibres. This appearance may be taken as evidence that the ventral horn cells have at one time been of good number and size. Chromatolysis of the nerve-cells, although it is to be found in practically every case, may be very scanty, or may be limited to a region of the cord or medulla. It is indeed rather surprising when examining a case in which there has been a steadily progressing weakness, to find

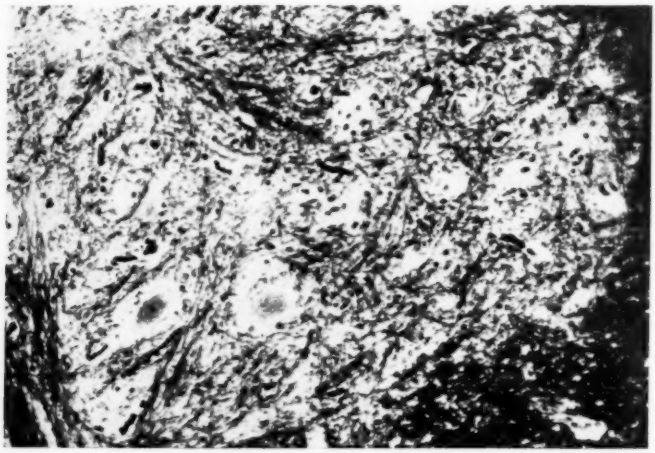

FIG. 1 (W. J., *Case* 1).—Area of the anterior horn of the lumbar enlargement at the level of L.3. Loyez stain for myelin. This demonstrates the empty beds from which the nerve cells have disappeared. Two large nerve cells are still present in their beds. The empty beds are filled with a fine reticulum formed by one or more neuroglial cells.

that only a small number of the nerve cells show any gross degenerative changes. But in such a case there is always a certain number of cells which are more rounded than normal, stain poorly with toluidin-blue and have an eccentric nucleus (fig. 2). "Ghost cells" are not uncommon, and may be more in evidence than cells in the earlier stages of chromatolysis, but they may easily escape detection, especially when, as is often the case, the nucleus is not included in the section. Then one sees a hyaline mass which can only be known to be a nerve cell from its position in the section, and by the arrangement of the surrounding tissues.

The amount of destruction or degeneration of the cranial nerve nuclei varies in different cases. They have not, indeed, been looked at in every case, but they have frequently been examined carefully with negative results. In our cases the hypoglossal nucleus was always involved and, indeed, gave more evidence of recent cell degeneration than any region of the spinal cord (fig. 3). Similar degeneration of the hypoglossal nucleus has been described by Baudouin, Rothmann, Griffiths and Spiller, Buzzard, Kaumheimer and Slauck. Baudouin also described chromatolysis in the abducens nucleus and Rothmann in the nucleus ambiguus, and Kaumheimer found the cells of the spinal

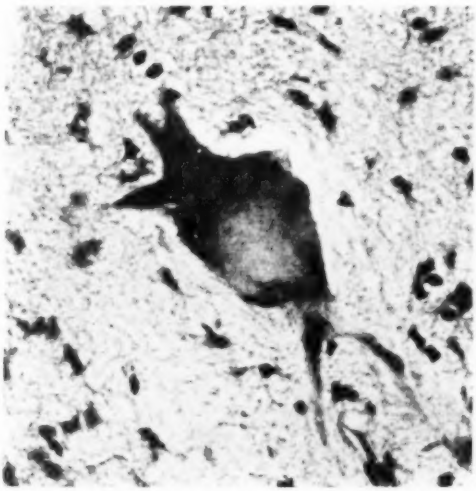

FIG. 2 (H. B., *Case* 4).—First lumbar segment; anterior horn cell undergoing chromatolysis and displacement of nucleus.

accessory nucleus to be atrophied. Archangelsky and Abrikosoff, de Villa, Foot and Brouwer and Schippers on the other hand found the hypoglossal nucleus to be normal.

(2) *Ventral roots.*—Atrophy with demyelination or degeneration of the ventral roots has been found in twenty-three of the twenty-five cases. They are not referred to by Huenkens and Bell or by Brouwer and Schippers.

Usually they have been noticed to be about half the size of the posterior roots and greyer in appearance. In our Case 3 the hypo-

glossal nerve also was noticed to be very thin, and in Buzzard's case the seventh, tenth, eleventh and twelfth cranial nerves were atrophied. Usually there is more demyelination than atrophy, a considerable area of the root on cross-section being devoid of myelin fibres, as is well seen in fig. 4. In spite of this intense demyelination there is often remarkably little evidence of recent myelin degeneration as shown by Marchi staining. We could find none in our cases. This may be a question of technical failure, as the Marchi method does not always succeed with material which has remained for a considerable length of time in formalin. But it seems more likely that it should be correlated with the scantiness

FIG. 3 (J. B., *Case* 3).—Cells of the hypoglossal nucleus.

of cells showing acute chromatolytic changes. In other words, the process is in most cases so slow that there is time for the complete removal of myelin from one degenerated fibre before another becomes affected.

(3) *Peripheral nerves.*—The descriptions of the condition of the peripheral nerves in amyotonia given by different authors vary more widely than do those of the central nervous system. Some have examined the nerves by the Marchi method only and in general have found slight degenerative changes. Others have used the Weigert-Pal method and have found conditions varying from the normal to severe degrees of demyelination. The majority have noted that the nerves

were thin, and that the number of fibres with thick myelin sheaths was below the average. In our cases it was impossible to say that the appearances of individual nerves were very far removed from the normal, but the nerves were certainly thin as compared with those of a child of the same age, and contained an unduly high proportion of fibres with very thin myelin sheaths (fig. 5). This may indicate a thinning of the sheaths of motor nerve fibres corresponding to the atrophy of the ventral horn cells, or it may mean that thinly myelinated fibres persist because they are afferent in function. Which of the two is the true view of the question, we are unable to state definitely, but we incline strongly to

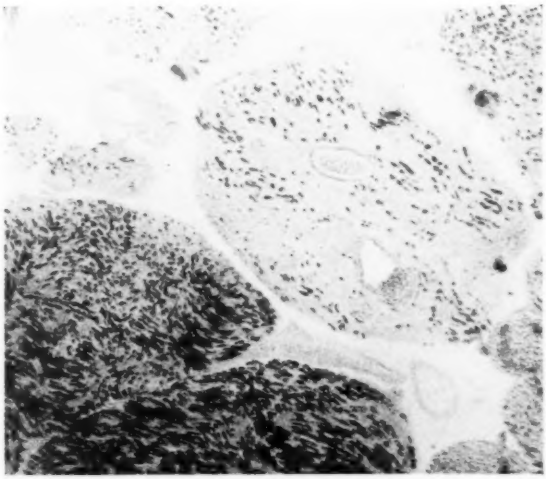

FIG. 4 (G. P., *Case* 2).—Cauda equina stained by the Weigert-Pal method; note the extreme degeneration of the anterior roots.

the latter hypothesis. There is in all mixed nerves a considerable proportion of very thin myelinated fibres which have been considered as sensory, and a general thinning of the nerve consequent on disappearance of a number of large motor-fibres would bring these fine fibres into prominence.

(4) *The muscles.*—The most striking similarity is found in the descriptions given of the muscles in all the cases examined with the exception of Spiller's, to which reference has already been made. The muscles are described as containing a few fibres of normal size and appearance and a much larger number of very small atrophied fibres consisting of little more

than chains of nuclei united by threads of sarcoplasm. Some of the larger fibres have been described as hypertrophied in a few cases, but the only authors who have found fibres of more than 100μ in diameter are Collier and Holmes, who described some up to 150μ in their biopsy material. Baudouin described fibres up to 100μ in diameter and we found one fibre of 90μ, but the majority of authors state specificially that no hypertrophied fibres or indeed fibres of more than 50μ diameter could be seen. It is impossible to say definitely what are the normal limits of width of muscle-fibre; they vary with the age and general nutrition of the patient. But in our experience fibres of less than 10μ or more than 50μ are not normally found.

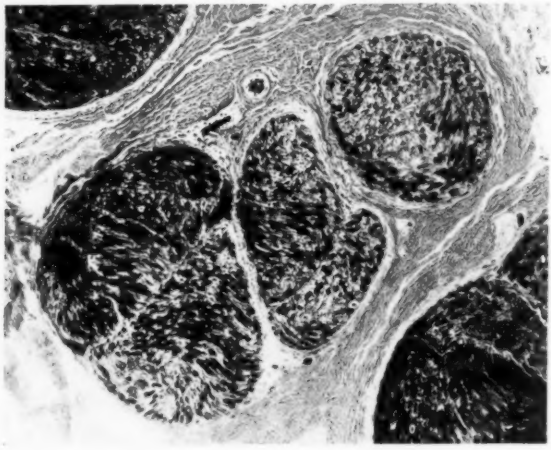

FIG. 5 (J. B., *Case* 3).—Sciatic nerve stained by the Weigert-Pal method. Three small bundles of fibres are seen demonstrating varying degrees of poverty in myelinated fibres. In one a large area of the bundle is quite devoid of myelin.

On the other hand, it is not uncommon to find fibres measuring up to 80μ in partially paralysed muscles a few months after an attack of poliomyelitis or in cases of partial recovery after nerve section. In the latter condition, indeed, we have found considerably larger fibres, up to 120μ. It is possible that the hypertrophy of fibres in such cases is due to the fact that those fibres, which have retained their nerve supply, or to which it has recently been restored, are called on for an extra amount of work owing to the paralysis of the other fibres. But some of these large fibres possess internal nuclei and show other evidence of abnormality, such as central vacuolation. It is therefore

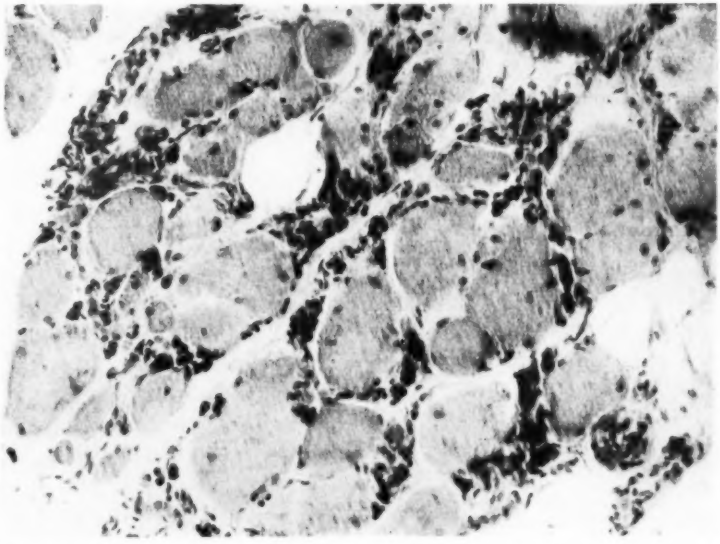

FIG. 6.—(Mr. Bristow's case of nerve section). Tibialis posticus muscle. Note the large size of some of the fibres, the masses of fine fibres and naked nuclei, and the fat replacement (× 200 diameters).

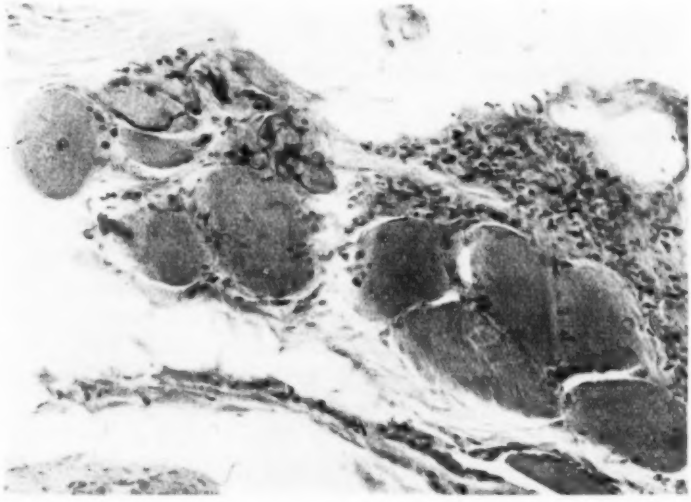

FIG. 7 (W. J., *Case* 1).—Tibialis anticus muscle. Note the areas of large and of small fibres, and the extensive fat replacement. (× 200 diameters.)

characteristic of neural atrophy. They are always scarce in myopathy, as in this condition the degenerating muscle fibres seem to disappear rapidly and completely, leaving behind only naked nuclei. There is no doubt that even in neural atrophy the paralysed fibres eventually disappear and are replaced by fatty or fibrous tissue. The sarcolemmal nuclei remain for some time after all trace of the sarcoplasm is lost, and may become clumped together or form chains between the fibres, and at this stage the appearances of myopathy and of neural atrophy can scarcely be distinguished.

But it is only in very long standing cases of amyotonia congenita that the muscles reach this stage. As a general rule the appearances seen in this disease—the large and small fibres in varying proportions and the slight interstitial fibrosis—resemble exactly what is found a few months after an attack of poliomyelitis, and are entirely consonant with the changes found in the central nervous system. What is, perhaps, of still more importance for our present purpose, is that the descriptions of the muscles in amyotonia and in Werdnig-Hoffmann paralysis tally in every detail, and that hypertrophied fibres and fat replacement have been described in some typical examples of the latter disease.

Discussion of Pathogenesis.

Of the various theories of the disease which have been formulated, the most important are those which presuppose a premature halt in the process of development, owing to which the nerve cells, nerves and muscle fibres of the neuro-muscular system remain in a fœtal condition. This theory has been stated by many in varying terms. Some regard the improvement which occurs in the disease as evidence of a progress towards maturity in the neuro-muscular mechanism. Others have described the condition in the muscles as resembling a fœtal stage. Collier and Holmes, however, consider that there are very definite differences between the muscles in amyotonia congenita and fœtal muscles.

The changes in the central nervous system certainly do not indicate a failure of development, but rather a decay of neurons. We do not find in Oppenheim's disease any evidence that the cord has remained in a fœtal condition, and although such appearances as antero-posterior elongation of the central canal and symmetrical fluting of the outline of the cord are not uncommonly found in the cords of infants, they form no part of this disease. It is true that we discovered a bi-nucleated nerve cell in the ventral horn in one of our cases, but this

impossible to lay down any absolute criterion, based on the histological appearance of a muscle fibre, as to whether we are dealing with a neural atrophy or a myopathy. A large amount of fat replacement and fibrosis has been considered to be evidence of myopathy, but it is certain that this frequently occurs also in paralysed muscles. We have found a high degree of interstitial fibrosis, in which individual fibres were isolated by strands of connective tissue, as early as eighteen weeks after an attack of poliomyelitis; and after wounds of nerves a still greater amount of fibrosis is often encountered. In this connection the examination of the muscles in a limb amputated six years after a wound of the posterior tibial nerve and artery has been particularly instructive to us. We are permitted to refer to this case by the kindness of Mr. Rowley Bristow, under whose care the patient was. In this case, some months after suture of the posterior tibial nerve, recovery of sensibility in the sole of the foot stopped and remained for more than a year at the stage in which every stimulus was appreciated as pain. "Any pressure on the sole of the foot was therefore painful and he could not walk or even stand with full weight on the limb" (Platt and Bristow). The muscles supplied by the posterior tibial nerve were in a condition of severe simple degeneration with large numbers of very thin fibres and clusters of naked nuclei. There was also a considerable amount of interstitial fibrosis and fat replacement. Among these atrophied fibres there were scattered large rounded fibres of an average diameter of 80μ, either isolated or in small clumps. Many of these fibres possessed internal nuclei (fig. 6). The picture corresponded so exactly to that which may be seen in fairly long-standing cases of amyotonia congenita that we have illustrated it in order to prove that any or all of the appearances seen in the latter disease may result from interference with the nerve supply of a muscle. This is certainly true for hypertrophied fibres with internal nuclei, which for some authors have been proof positive that the condition was primarily myopathic.

In our 13-year-old case atrophy of many of the muscle-fibres had gone on to complete disappearance and replacement by fatty tissue. In the leg muscles, indeed, much of the tissue was almost entirely fatty, with only a few isolated muscle-fibres running through it. But in every muscle examined there was in some part of the section a region where minute shrunken fibres predominated. It is known that muscle fibres may persist—as fine sarcoplasmic threads joining chains of nuclei—for months and even for years after loss of their nerve supply, and areas full of fine fibres of this kind are so common in paralysed muscles as to be

to birth injury, or to any one of many intra-uterine diseases, among which fœtal poliomyelitis has to be considered. Marburg, in fact, long ago suggested that some cases diagnosed as amyotonia congenita were in reality fœtal poliomyelitis, and Batten has provided indisputable evidence that the latter disease can occur *in utero*. For the present, however, Marburg's hypothesis remains unproved.

What seems to us of definite value is the clear proof which an examination of the post-mortem material of Oppenheim's disease has furnished, that between this disease and that described by Werdnig and Hoffmann there is no anatomical distinction, since both are dependent on degeneration of the lower motor neuron.

Description of Personally Examined Cases.

Of the four cases of infantile muscular atrophy to be described, the first three cases were diagnosed clinically amyotonia congenita, whilst the fourth (H.B) was designated Werdnig-Hoffmann paralysis.

We are indebted to Dr. Risien Russell, Dr. Collier, Dr. Bernard Myers and Dr. Still, under whose care they were, for permission to publish these cases.

Case 1.—W. J., aged 13 (male), was admitted to the National Hospital on July 26, 1921, under Dr. Risien Russell, with the complaint that he had been unable to use his limbs properly since birth. The patient was the eldest of the family; the youngest son and fourth child suffered from the same condition and was a patient in the National Hospital; a sister, aged 5, was well, and able to run about.

On examination, the boy was small for his age but of normal intelligence. All the cranial nerves, except the twelfth, were normal. The tongue was not protruded well and was atrophied, as evidenced by the presence on it of large dimples. The spine showed a marked scoliosis with the convexity to the right. All arm movements were very weak, but equal. Grips were very weak. In the legs very little movement was possible. Contractures were present at the knee-joints. There was no power of extension at the knees, whilst flexion and extension at the ankles were poor, but equally strong on the two sides. All the deep tendon reflexes were absent. The cremasterics were present, but the abdominals were absent. Sensation was normal, except for an increased tolerance to faradism.

Death took place on October 13, 1921.

Post-mortem notes.—The body was very small and thin, and showed contractures of the lower limbs. The left leg especially was flexed at the hip, knee and ankle, and could not be straightened out. This was not due to post-mortem rigidity, of which no trace could be made out. The spine was curved

was the case diagnosed as Werdnig-Hoffmann paralysis. On the other hand, we have indisputable evidence of neuronal degeneration in the presence of chromatolytic cells, and of the "empty beds" to which reference has been made by several writers.

The pathological evidence is, therefore, altogether in favour of the disease being due to a degeneration of the neurons of the ventral horns, a process which may begin either before birth or within the first year of life, and which may be either rapid or slow in its progress or may even cease to advance. Whether a degenerating neuron may recover we do not know. It is impossible to be certain on this point from the material at our disposal, as the appearances seen in a nerve-cell or muscle-fibre during the process of recovery are not in any way distinctive. But the clinical histories of the cases suggest that the improvement which may take place resembles the increase of function in a paralysed limb, which may result from re-education, rather than that which follows a restoration of the nervous mechanism to a healthy condition.

Two points remain in doubt. The first is whether there exists a distinct type of disease corresponding pathologically to the case of Councilman and Dunn, that is to say, with changes in the muscles similar to those in Werdnig-Hoffmann paralysis but with no changes in the central nervous system. Some authors suppose that the affection in the muscle precedes that in the cord; but if this were true for that part of the neuro-muscular mechanism which is first affected, it does not appear to be true for parts attacked later, as for example the hypoglossal nucleus and the tongue; for in them the evidences of neuronal degeneration are usually more prominent than the muscular atrophy. It may be that in this disease the peripheral part of the neuron is first affected, and that the degeneration of the intramuscular nerve-twigs which Councilman and Dunn found was the earliest expression of this pathological process. Or it may be, as we have already suggested, that the changes in the central nervous system in their case were not so obvious as the degree of paralysis would have led them to suppose. If this hypothesis is the correct one their case does not stand alone, but rather takes its place at one end of the series of twenty-five post-mortem cases, in which the degree of alteration found in the central nervous system varies greatly.

The other question is whether, as Krabbe has postulated, there exists a type of case of which we have no post-mortem records; a non-familial, congenital type, in which steady improvement goes on to complete recovery. Symptoms of atony and weakness at birth may be due

with lordosis and considerable scoliosis, and the chest was asymmetrical. The size and appearance of the boy was that of a child of 6 or 7 years.

The brain and spinal cord were removed. The brain was generally hyperæmic, especially over the posterior half of the hemispheres. The anterior roots were thin and greyish by comparison with the posterior roots.

In the chest, the right lower lobe was the seat of some incomplete collapse, and was congested, as was also the lower lobe of the left lung. The upper lobes of both lungs were healthy. The heart was healthy, weighing 123 grm. The thyroid was small, though apparently normal for his size, weighing 8 grm. The thymus was evident but not abnormally large, weighing 14 grm. The other organs of the body appeared healthy. The right suprarenal weighed 4 grm., the right kidney 63 grm., and the spleen 49 grm. The testes were very small, about the size of a haricot bean and weighed 1 grm.

All the muscles were very pale and looked fatty. Their bulk was very small indeed, much less than appeared on looking at the boy, as there was everywhere quite a thick layer of fat under the skin. Certain muscles, e.g., the soleus, were rather more red than others, but no muscle had the normal colour.

Pieces of various muscles and nerves were taken for microscopy.

Microscopic examination.—The cerebral cortex, mid-brain and pons presented no abnormalities. In the medulla there was a most striking lack of cells in the hypoglossal nucleus. In many sections only one or two cells of this nucleus could be found and in no section did the number approximate to the normal. No degenerative changes were seen in those present but they were smaller than normal.

In the spinal cord, stained by the Nissl method, the anterior horn cells were found to be diminished both in size and in number throughout the cord. Otherwise they appeared normal, except for one cell at the level of the fourth to fifth lumbar segment, which showed eccentricity of the nucleus. Clarke's column was normal.

No abnormalities were seen in the blood-vessels by the hæmatoxylin-van Gieson method and the Victoria-blue method did not demonstrate any increase in neuroglia.

In sections of the spinal cord, stained by the Weigert-Pal method and counterstained by carmine, a very characteristic change was noted, to which reference has already been made. At first sight it looked as though a large number of motor nerve cells were present, owing to the presence of spaces in the myelinated network, which corresponded in number and arrangement to the position of these cells. But on examining the sections under a higher power it was seen that the majority of these cell beds appeared empty, while only a few contained normal-looking ganglion cells and others contained small shrunken cells which did not nearly fill the cell beds. It is noteworthy that none of the empty cell beds was as large as those which contained the more normal ganglion cells. It appeared, therefore, as though they had shrunken down after the disappearance of the nerve cells from them.

These spaces in the myelin network have been described as "empty beds" by Hoffmann, Brouwer and Schippers, Slauck, and others, but as Kaumheimer pointed out, and as is clearly seen in fig. 1, they are in reality filled by neuroglial tissue.

The anterior roots were greatly altered. In the cervical region they were small and considerably demyelinated, contrasting strongly with the normal posterior roots. In the lumbar region there was a similar demyelination of the anterior roots, and many strands appeared as irregular rounded zones measuring 10 μ to 30 μ across, which contained fine, brown-staining granules, but no myelin. The myelinated fibres, on the other hand, were much smaller, measuring from 6 μ to 10 μ across. The Marchi method gave no evidence of any tract degeneration in the cord.

Peripheral nerves.—The vagus, median, ulnar and sciatic nerves were examined by the Weigert-Pal method. The vagus was composed of a very large number of small fibres and a few larger ones, but there was no abnormal spacing of the fibres. The median nerve was small and the number of small fibres was greater than normal, but individual bundles were well filled with myelinated fibres. In the ulnar there was a very large proportion of small, finely myelinated fibres, but no more unmyelinated fibres were present than are found in a normal nerve. In the sciatic, the proportion of small, finely myelinated fibres was also great, but again very few were demyelinated. The separation of individual fibres from one another was, however, wider than in a normal nerve.

Muscles.—Sections of the following muscles were examined: Tongue, biceps, triceps, flexor longus digitorum, rectus abdominis, quadratus femoris, soleus, tibialis anticus and peroneus brevis.

In the tongue the muscle-fibres were very loosely arranged, and apparently many of them had disappeared and had been replaced by fatty tissue. In many places, by far the greatest part of the section was occupied by fatty tissue, in which ran bundles of from ten to twenty fibres. The remaining fibres looked fairly healthy and did not seem to have any excess of nuclei. In addition to these normal-looking fibres, there were in many places groups of very fine fibres, measuring 6 μ to 8 μ in diameter and containing many nuclei. These fine fibres were not so much in evidence in the tongue as in some of the other muscles in this case. In some of the finest fibres, cross striation was very difficult to see, but in the majority it was quite obvious. No fibres measuring more than 50 μ were seen.

In the arm muscles there seemed to be less disappearance of fibres, and many large bundles of fibres were present, the only abnormality in which consisted in a slight excess of sarcoplasmic nuclei. Between these were many bundles of fibres so atrophied that in many of them only the nuclei remained and clumps and chains of these nuclei filled the field. A few fine threads, which still retained their cross striation, could still be seen here and there connecting these nuclei. There was a considerable amount of fat replacement. The flexor longus digitorum was considerably more affected than either the biceps or the triceps, in which many fields appeared perfectly normal.

The rectus abdominis resembled the tongue in the amount of fat replacement and the relatively small number of atrophied fibres, but here and there were areas where the majority of the fibres were atrophied and nothing but the nuclei remained. Here, too, the larger fibres showed no abnormality.

In the leg muscles, the disappearance of fibres and replacement by fat had reached a maximum, and by far the greatest part of the sections consisted of fibrous and fatty tissue in which fairly normal-looking fibres ran in small bundles and sometimes even as single fibres. In addition to these, there were collections of sarcoplasmic nuclei and shrunken fibres, but they were much less in evidence than in the arm muscles. The degree of atrophy and the number of shrunken fibres and bare nuclei varied from one part of a muscle to another,

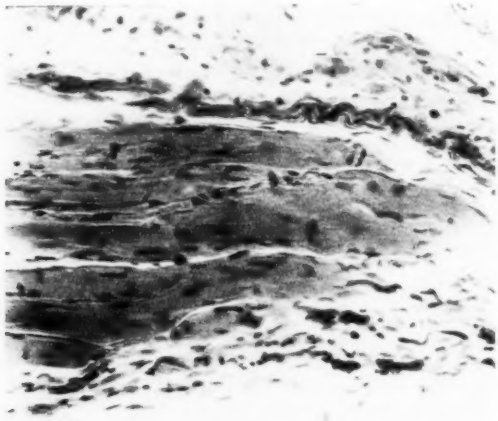

FIG. 8 (W. J., *Case* 1).—Longitudinal section of peroneus brevis. These are a few of the more healthy fibres surrounded by a narrow zone containing fine fibres and naked nuclei in a large area of fatty tissue. (× 200 diameters.)

so that even in a muscle, the greater part of which was replaced by fatty tissue, some strands could be found measuring 2 or 3 mm. in thickness, which consisted almost entirely of normal muscle-fibres.

Case 2.—G. P., male, aged 8 months, was admitted to the National Hospital on August 15, 1924, under Dr. Collier, on account of his "head flopping about," a condition which had been present since birth. He had been a full-time child, and was the only one in the family. There had been no miscarriages.

On examination he was found to be a healthy and plump baby, difficult to wean, but who could laugh, was easily amused, and was also able to cry effectively. The cranial nerves showed no abnormality, except that the head could not be held up. It flopped about from side to side, and if the child were turned upside down it flopped in every direction. The arms had not been seen

to move. There was no obvious wasting. No attempt was made to grasp objects. Slight hyperextension was possible at the elbow, whilst the fingers could be greatly hyperextended. The back muscles were weak, and sitting up an impossibility. The head could easily be flexed between the legs. Breathing was largely abdominal, with expansion of the lower part of the chest (? diaphragmatic). No voluntary movements were observed in the legs, which could be shaken about as if completely paralysed. The feet could almost be dorsiflexed against the tibiæ.

There was no apparent wasting of the leg muscles.

Sensation appeared normal, as when the hands and feet were pricked the face showed pain, although the limbs were not moved. The deep reflexes were all absent. The abdominals were present, whilst the plantars, not always obtainable, gave flexor responses.

On September 9, 1924, he was observed to move his toes slightly and to turn his head from side to side a little.

On October 10 the breathing was laboured, and there was no sign of intercostal action. Death took place on October 24 at the age of 10 months.

Post-mortem notes.—The body was that of a well-nourished baby.

The muscles were small and pale. Such flat muscles as the sterno-mastoid, serratus magnus and deltoid were represented only by thin layers. Various muscles with the sciatic and posterior tibial nerves were removed for section.

In the chest the right lung was entirely collapsed, so that each of its three lobes sank in water. The left lung showed one or two areas of collapse in its lower part. The chest itself was hollowed laterally and expanded at the lower ribs.

The heart appeared healthy and the aorta normal. The thyroid and trachea were normal. The abdomen was distended. The liver showed pale stripes on its anterior surface, corresponding to the ribs and obviously due to pressure by them. The spleen was small and appeared normal. The bladder was distended. The wall was thin and white and showed no suggestion of muscular tissue in it. The testes were not examined.

Microscopic examination.—The cerebral cortex, mid-brain and pons showed no abnormalities.

In the medulla, in nearly every section examined, one cell of the hypoglossal nucleus presented chromatolytic changes. In some, these changes had reached a point at which only the outline of the cell, with a shadowy nucleus at the periphery, could be recognized. The number of cells in the nucleus was diminished, though not greatly so.

The spinal cord, stained by the Nissl method, showed throughout its length diminution in number and size of the anterior horn cells. In the cervical region a few cells of normal size were seen, but the pallor of the Nissl granules seen in them contrasted with the neighbouring smaller cells, the granules of which took the stain well. The postero-lateral group was less affected than other groups. At the level of the first thoracic segment a " ghost cell," i.e., one in the stage of acute degeneration just prior to disintegration, was found. Clarke's column was everywhere normal.

At the level of the third lumbar segment degenerative changes in the anterior horn cells were especially evident in the antero-lateral group, whilst the diminution in number of cells at this level was striking.

In the sacral region, at the level of the first and second segments, only about twelve cells were seen in the antero-lateral group instead of the normal thirty, and many of these showed acute degenerative changes and some vacuolation.

No changes were seen in the blood-vessels by the hæmatoxylin and van-Gieson method, and no increase in neuroglia was shown by the Victoria-blue method.

By the Weigert-Pal method, the cord itself was normally myelinated but in the cauda equina there was considerable loss of myelin. In the region of the anterior horns throughout the cord, but particularly at the level of the first lumbar segment, the myelinated fibres defined large empty spaces, out of which the cells had evidently disappeared, leaving behind them "empty beds," similar to those described in Case 1.

The anterior roots were all small compared with the posterior roots and were poorly myelinated.

The Marchi method gave no evidence of any tract or root degeneration.

Peripheral nerves.—In the sciatic nerve the number of small and thinly myelinated nerve fibres was greatly in excess of the normal. The large fibres, although diminished in number, were well myelinated. There was also a much wider separation of individual myelinated fibres from each other than in a normal nerve.

The median or ulnar nerve showed the same picture as the sciatic, with, in addition, a definite fibrosis.

Muscles.—Longitudinal and transverse sections of the following muscles were examined: Sterno-mastoid, pectoralis major, subscapularis, teres major, deltoid, infraspinatus, intercostals, diaphragm, erector spinæ, serratus magnus, biceps femoris, semitendinosus, gastrocnemius and tibialis posticus.

A summary of the findings is given: The outstanding feature of all muscles was the advanced atrophy of individual fibres. The average diameter of the fibres was between 5 μ and 20 μ, and no fibres exceeding 50 μ in diameter could be found. In some bundles the fibres had become shrunken greatly, so as to leave only chains of nuclei as evidence of their former existence, but cross striation was well preserved in all recognizable fibres. Comparatively normal and atrophied fibres occurred together in the same bundle, except in the subscapularis and teres major, in which there was a tendency for them to be separated into distinct bundles. In some muscles there was considerable fat replacement, but internal nuclei and longitudinal splitting of fibres could nowhere be found. In the diaphragm, although the individual fibres were small, of 15 μ to 20 μ diameter, they were uniform in size, and may be regarded as normal for this muscle.

Case 3.—J. B., aged 3 (female), was first admitted to the Royal Waterloo Hospital under Dr. Bernard Myers in September, 1925, for inability to sit up,

combined with an abnormal mobility of the limbs. The condition was said to have been noticed first when the child was 6 months old, but may have been present earlier.

On examination, the child was listless but otherwise well. The back was a little weak and showed a moderate general kyphotic curve. On holding her by hands placed in the axillæ, the shoulders slipped up. The intercostal muscles were acting normally at this time. The deep tendon reflexes were diminished, the abdominals were normal and the plantars were flexor.

The optic discs were normal, and no macular changes were observed.

The Wassermann reaction of the blood was negative.

The electrical reactions showed that the child could tolerate a fairly strong faradic current with comfort, except on the face, where there was a normal reaction, whilst with galvanism ACC. was greater than KCC.

In November, 1925, she had an attack of pneumonia, from which she appeared to recover, to have another attack in February, 1926. In spite of the bases of both lungs being involved, she recovered from this attack also, and in April, 1926, her general muscular condition was reported to be improved.

From June 1 to October 15, 1926, she was in Tooting Grove Hospital with nasal diphtheria. On re-admission to the Royal Waterloo Hospital, the child looked well and was happy. The back was more floppy than before she had diphtheria, and seemed to become more so during the rest of her stay in hospital. The intercostals did not function so well as they had done before. Movement of all limbs was very free. Both feet were held fully extended with the toes turned towards the soles. She seemed to have full power over her tongue in June, but was not seen to protrude it after the attack of diphtheria. In December, 1926, she contracted scarlet fever, from which she died in the South Western Fever Hospital, where, owing to the kindness of the medical staff, a post-mortem examination was made by Dr. Greenfield.

Post-mortem notes.—The body was that of a rather plump child. The fat was very firm, so that when cut it retained a sharp edge. The muscles were small but not pale, the triceps were larger than the biceps, whilst the the biceps cruralis was also small and the erector spinæ very thin. The intercostal spaces were translucent. The brain and spinal cord were removed. The roots of the twelfth cranial nerve and all the anterior roots were very thin, and greyish-pink in colour, contrasting sharply with the well-developed posterior roots.

In the chest, the lungs were considerably collapsed, and there was some early broncho-pneumonia at the bases. The chest cavity was very small, the diaphragm rising high in the chest. Portions of the lungs sank in water.

The heart was healthy. There were no evident bronchial glands. The intestines, from the duodenum throughout the jejunum, contained black altered blood, a little of which was also present in the stomach. No ulceration of the stomach or duodenum could be discovered. The liver was very large and pale; it floated in saline. The spleen was slightly enlarged and rather soft.

The kidneys and suprarenals were healthy. The thymus was fairly large and pinkish. The uterus and ovaries were normally infantile.

Pieces of sciatic, ulnar and median nerves, and of biceps (leg), biceps (arm), and triceps muscles and tongue were kept for microscopy.

Microscopic examination.—The cerebral cortex, mid-brain and pons appeared normal. In the medulla, the twelfth nucleus showed at almost every section, one cell with acute degenerative changes—either gross loss of chromatic granules or loss of the central or intermediate zone of granules. Many other cells were rounded in form. These changes were most intense at the level where the central canal of the cord opens out into the fourth ventricle, and for $\frac{1}{5}$ mm. above and below this level. The cells of the nucleus were rather more scanty than normal. In the nucleus ambiguus there were very few cells. These were rounded and small with large central clumps of chromatin.

Throughout the spinal cord the Nissl method revealed a great diminution in the number of anterior horn cells. In some sections from the first thoracic segment not one single such cell could be seen.

In the cervical region, at the level of the first cervical segment, a few cells presented chromatolytic changes. At the level of the fourth cervical segment there was an area of perivascular infiltration with small round cells in the grey matter of the posterior horn and postero-mesial fissure. This infiltration was also found at the level of the eighth cervical segment. Here there was also seen a chromatolytic anterior horn cell. In this segment the postero-lateral group contained more cells than in other segments.

Throughout the thoracic segments the paucity of anterior horn cells was obvious, whereas Clarke's column and the cells of the lateral horn were normal in number and appearance.

In the lumbar region the diminution in cells was even more striking. At the level of the second lumbar segment the postero-lateral group of anterior horn cells consisted of only 10 large cells instead of 26; at the level of the third lumbar, practically none instead of the normal 36, whilst at the level of the fourth lumbar the antero-lateral group contained 3 instead of 25 and the posterio-lateral 2 instead of 50.

By the Weigert-Pal method the cord itself showed no demyelination, but the anterior roots were extremely small and appeared greatly demyelinated, contrasting thus with the normal posterior roots. Here also very numerous "empty beds" were seen.

By the Victoria-blue method there was no evidence of neuroglial overgrowth in any part of the cord. The Scharlach R. method showed no pigment in the anterior horn cells and neither this nor the Marchi method revealed any trace of tract degeneration.

Peripheral nerves.—The ulnar and sciatic nerves were examined by the Weigert-Pal method. In the ulnar nerve some fibres were definitely demyelinated, and there were large numbers of very small, finely myelinated fibres. All the fibres were more widely spaced than in a normal ulnar nerve, and there was some slight but definite fibrosis. In the sciatic nerve there was a larger

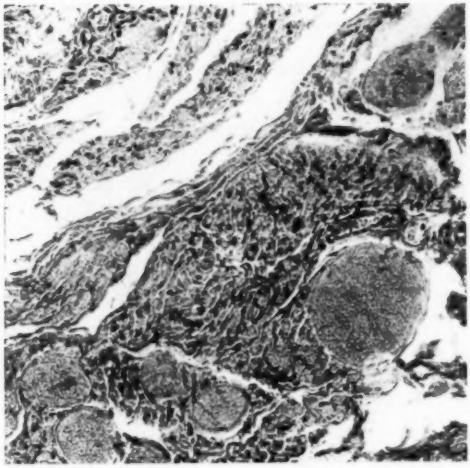

FIG. 9 (J. B., *Case* 3).—Transverse section of the triceps muscle. This illustrates the largest fibre (90 μ) found in any muscle (× 200 diameters).

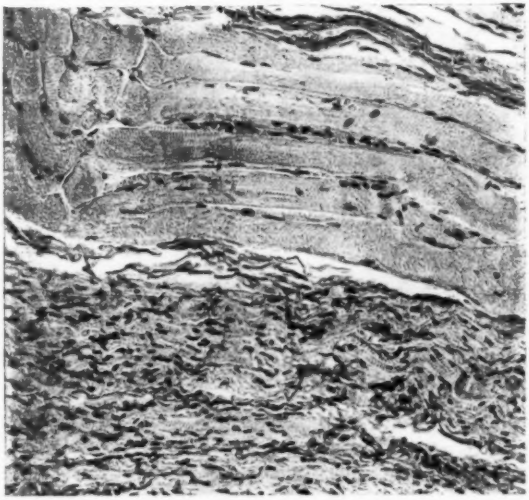

FIG. 10 (J. B., *Case* 3).—Longitudinal section of the biceps brachialis. A band of normal fibres and a band of atrophied fibres are seen. (× 200 diameters.)

proportion both of small myelinated fibres and of demyelinated ones than in a normal nerve, but no fibrosis was observed (fig. 5).

Muscles.—Sections of tongue, biceps (brachialis and femoris) and triceps were examined. The tongue appeared normal. There were no atrophied fibres, all the fibres being about the same size, from 12 μ to 25 μ in diameter. No fat replacement was observed, nor was there any increase in fibrous tissue.

In the other muscles there were large numbers of atrophied fibres, the smallest of these being under 4 μ in diameter. Larger fibres with a diameter up to 60 μ were also present, especially in the triceps, where one fibre with a diameter of 90 μ was seen (fig. 9). In general, the small fibres outnumbered the larger ones. There seemed to be no proliferation of sarcolemmal nuclei. No increase in fibrous tissue had occurred, but there had been some fat replacement.

Case 4.—H. B., a male, aged 10 weeks, was admitted under the care of Dr. Still to the Hospital for Sick Children, Great Ormond Street, in October, 1925, for inability to use the limbs.

The child had seemed quite normal at birth, though his movements had never been so vigorous as those of his sister. At the age of 6 weeks it was noticed that he had stopped kicking. His wrists dropped, and soon after he became unable to hold his head up.

There was no history of any similar trouble in the family. This child was the younger of two children, of whom the elder, a girl aged 16 months, was not yet able to walk. Examination revealed a complete flaccid paralysis of arms and legs. The intercostal muscles also, if not completely paralysed, were very weak. The back muscles were also weak. In the arms, the only remaining movement was that of grasping. Even this was very weak with the left hand, and almost impossible with the right.

In the legs, slight flexion and extension of the ankles were possible, as well as slight movements of the toes.

Some facial weakness was observed when first examined, but this became less pronounced whilst in hospital and disappeared entirely before death.

The other cranial nerves were normal. The deep reflexes were all absent. There was no sphincter disturbance. Sensation appeared normal as far as could be ascertained. The mental state was that of a normal child of ten weeks.

Whilst in hospital the child developed broncho-pneumonia, and died six weeks after admission.

Post-mortem examination.—The body was that of a well-nourished child. The chest was flattened laterally, and the abdomen was slightly prominent. The legs were covered with about $\frac{1}{2}$ in. of fat. There was also a good layer of fat over the arms, chest and abdomen.

The brain and spinal cord were removed. The motor roots from the twelfth cranial nerve downwards were very thin and grey and contrasted strongly with the well myelinated dorsal roots. Otherwise there was no abnormality in the brain or spinal cord.

The tongue was rather wasted. The larynx and trachea were normal. The thymus was pink and fleshy but not unduly large. It weighed 11 grm. In the lungs the middle and lower lobes of the right lung and the lower lobe of the left lung were almost entirely collapsed. The lower lobe sank in water, whilst the middle lobe was held to the surface by the anterior edge, which contained some air. The upper lobes were fairly well aerated. The heart, liver and spleen were healthy. The suprarenals were thin-walled capsules. The kidneys were normal and preserved a fœtal lobulation. The stomach and intestines were healthy Pieces of various muscles and nerves were taken for microscopy.

Microscopic examination.—The cerebral cortex, mid-brain and pons were normal. In the medulla, several cells of the hypoglossal nucleus were in a condition of central chromatolysis. The number of cells in the nucleus was diminished though not greatly.

Spinal cord: In the upper cervical region the Nissl method revealed little diminution in the size or number of anterior horn cells. At the level of the third cervical segment there was evidence of degeneration in one anterior horn cell. From the level of the fifth cervical segment downwards throughout the cord the anterior horn cells were greatly diminished both in size and number. In the sixth, seventh and eighth cervical segments, in which the anterior horn cells are normally specially large and numerous, there was only on an average one large cell on each side of each section, though there were considerable numbers of small cells which were normal in appearance.

Clarke's column was everywhere normal. At the level of the twelfth thoracic segment a binucleated nerve cell was seen in the anterior horn and another cell in a condition of severe chromatolytic degeneration.

In the lumbar region the same striking picture of poverty in large anterior horn cells was seen. At the level of the second lumbar segment only two large cells were found in the antero-lateral group and only four in the postero-lateral group. In addition, at the level of the third and fourth lumbar segments, cells so degenerated as to merit the title of "ghost-cells" were found.

The hæmatoxylin van-Gieson and Victoria-blue methods showed no neuroglial overgrowth or changes in the blood-vessels. The Scharlach R. method gave a negative result. By the Weigert-Pal method the cord itself appeared well myelinated throughout its length, but the anterior nerve roots were definitely less well myelinated than the posterior roots. Numerous empty beds were found as in the other cases. In comparison to the posterior roots the anterior roots were also smaller than normal. The Marchi method did not reveal any tract degeneration.

Peripheral nerves.—The sciatic, median, and ulnar nerves were examined.

The proportion of small to large fibres was certainly increased in sections of all nerves examined. There was, however, no gross demyelinization, but many small fibres were more poorly myelinated than in the nerves taken as normal controls.

Muscles.—Longitudinal and transverse sections of the following muscles

3½ years, 10 months and 4 months, the microscopical appearances were almost identical in the four cases, the only dissimilarity being the remarkable amount of fat and fibrous tissue replacement in the muscles in Case 1.

(1) In the medulla of all the cases some diminution in the number of cells in the hypoglossal nucleus was noted, whilst in one (Case 3, J. B.), there was also a paucity of cells in the nucleus ambiguus.

In three cases acute degenerative changes were seen in the residual cells of the hypoglossal nucleus. In the other (Case 1, W. J.), which reached the age of 13 years, it is reasonable to suppose that many cells had passed through the more acute stages of degeneration and had disappeared completely before death. Certainly in this case there was a far greater loss of cells in the hypoglossal nucleus than in the others.

That there was no evidence of recent cell degeneration in the spinal cord in Case 1 (W. J.) is hardly remarkable when we consider the long duration of the case. It agrees with the absence of chromatolytic changes in the twelfth nucleus in this case to which reference has just been made.

(2) In the spinal cord there was a similar but more striking diminution in the number and size of the anterior horn cells, with, again in the same three cases, very definite chromatolytic changes in some of those remaining.

(3) The anterior nerve-roots were all very small as compared with the normal posterior roots and showed considerable loss of myelin.

(4) In the peripheral nerves the most obvious abnormality was the unduly high proportion of minute, finely myelinated fibres. Comparison with the corresponding nerves of a child aged 6 months, who had died from tuberculous meningitis, was made to confirm this. The individual fibres were generally packed less closely together than in normal nerves, giving the appearance of an actual diminution of the number of fibres in each bundle. There was no relative increase in the number of non-myelinated fibres.

(5) The muscles all showed the features of a simple atrophy. Tiny fibres, below 4 μ in diameter, were found in every muscle examined, except in those of the diaphragm, which in all cases appeared normal. Nowhere were large hypertrophic fibres seen; fibres above 50 μ were very rare; the largest fibre and the only one of that size seen was 90 μ. Transverse striation was visible in the smallest recognizable fibres. Fat replacement was evident in many muscles, particularly in those of the most long-standing case, but there was comparatively little increase

were examined: Sterno-mastoid, trapezius, pectoralis major, deltoid, triceps, flexor carpi ulnaris, erector spinæ, diaphragm, gluteus, rectus femoris, biceps femoris, gastrocnemius, tibialis anticus and peroneus longus.

The findings are summarized below:—

Extreme smallness of some of the fibres was the chief feature seen in all muscles. In many muscles these fibres were so minute that we were unable to measure their diameter; it was much below 4 μ. In some cases the fibres had so far atrophied that they were represented only by chains of nuclei. In no muscle were fibres over 40 μ in diameter found. The largest fibres were those of the sterno-mastoid, which measured from 30 μ to 40 μ, but even in this muscle minute fibres about 4 μ in diameter were also present. In the

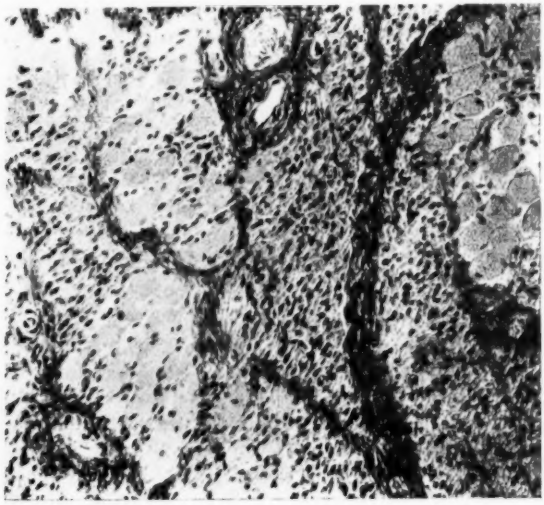

FIG. 11 (H. B., *Case* 4).—Transverse section of the tibialis anticus. Note the large amount of fibrosis.

diaphragm, on the other hand, although the fibres were small, between 15 μ and 25 μ in diameter, they were all approximately of the same size and no very small fibres were seen.

There was remarkably little fat replacement in these muscles and it cannot be said that there was any true fibrosis. Longitudinal splitting of fibres was not observed.

SUMMARY OF MICROSCOPICAL APPEARANCES.

In reviewing the anatomical findings in these cases, one cannot but be struck by the fact that notwithstanding the differences in the course of the disease, the children dying at the respective ages of 13 years,

Buzzard ..	1911	,,	10/52	No	,, ...	V.H.C. much diminished in number, chromatolysis and "ghost cells"	Cells of xii nucleus diminished in number with chrom.	vii, x, xi and xii nerves and anterior roots of cord small	Slight Marchi degeneration in a few fibres	Normal and atrophied fibres
Archangelsky and Abrikosoff	1911	,,	6/12	Yes	,, ...	V.H.C. very few in number and very small	Normal ..	Very small and pale	Fibres very small	Small fibres 2·4 μ; large ones 18-24 μ
Concetti ..	1913	,,	8/52	No	,, ...	V.H.C. very small and scarce	Normal; dim. in size and no. of gangl. cells in Rolandic area of cortex and of Purkinje's cells in cerebell.	Thin ..	Normal ..	Atrophied, normal and hypertrophied fibres
Foot	1913	,,	3/12	Yes	3 of 8 children affected	V.H.C. diminished in size and number; acute degenerative changes	Degeneration in formatio reticularis and pyramidal tract	Very pale ..	Less than half the fibres normally myelinated	Small fibres 3·5 μ; large ones 20-50 μ; fat and small round cell infiltration
Kaumheimer ..	1913	,,	4/12	No	Non	Diminution in size and number of v.h.c. with degenerative changes; "empty beds"	Atrophy of cells of xi and xii nuclei	Slight degeneration	Diminution in myelinated fibres, c.t. increased	Most fibres atrophied, some large; nuclei and c.t. increased; internal splitting of fibres
Brouwer and Schippers	1914	,,	4½	Slight	Doubtful ..	Very few v.h.c.; "empty beds"	Normal ..	—	—	Atrophy of most fibres; no hypertrophied fibres; nuclei increased; fat and c.t. replacement
Villa, de ..	1916	,,	3	No	Non	V.H.C. diminished in size and number; ? slight chromatolysis	,, ..	Thin ..	Normal ..	Most fibres small; a few larger than normal
Wälle and Hotz	1917	10/52	6/12	Yes	,, ...	V.H.C. greatly diminished in number; all stages of acute degeneration in them and in post. horns		Normal in size but much demyelinated	,, ..	Great atrophy of fibres; nuclei and c.t. greatly increased; little fat replacement
Lange, de ..	1919	Birth	3 12	No	1 younger b. affected d. at 5/52	V.H.C. greatly diminished in size and number	—	Small and degenerated	Small and irregularly myelinated	Most fibres atrophied, isolated large ones; nuclei and c.t. increased
Krabbe ..	1920	,,	6/12	V. slight	Brother 6 yrs. younger aff.	V.H.C. diminished in size and number; some chromatolysis	—	Degenerated	—	Size of fibres varied but none hypertrophied; nuclei relatively increased

AMYOTONIA CONGENITA.

Cases with Autopsies.

Author	Date	Age in years at: Onset	Age in years at: Death	Improvement	Familial or non-familial	Spinal cord	Medulla	Anterior roots	Peripheral nerves	Muscles
Beevor ..	1902	Birth	8/52	Slight	4 of 8 children affected	V.H.C. very few and small; Marchi degeneration post. cols.	—	Atrophied ..	Degen. fibres in brach. plexus	Fibres 8-24 μ
Spiller ..	1905	5/12	1 11/12	—	Non	Normal	—	Normal ..	Normal ..	Fibres small and hyaloid; fat and c.t. increased in small foot muscles
Baudouin ..	1907	Birth	5/12	No	.. .. ..	V.H.C. diminished in size and number	Chromatolysis in vi and xii nuclei	Small ..	Many fibres not yet myelinated	Small fibres 6-8 μ; large ones up to 100 μ; internal nuclei present
Collier and Holmes, G.	1909	..	7	Yes	.. .. ..	V.H.C. less than one-third, normal number.	—	Very slender; much demyelinated	Myelin sheaths of a few fibres very thin	Small fibres 6 12 μ; large ones 100-150 μ; nuclei increased; splitting of fibres
Lereboullet and Baudouin	1909	..	11/12	No	.. .. ..	Normal	—	Normal ..	—	Large and small fibres; sclerosis in neck muscles
Rothmann ..	1909	..	5/12	V. slight	1st child ..	Cord small, very few v.h.c.	Chromatolysis in xii nuclei	Much atrophied and demyelinated	Very thin but many large fibres. c.t. increased	Nuclei and c.t. increased
Batten ..	1911 (1)	2/52	4/52	No	.. .. ..	V.H.C. normal in size and number but some chromatolysis	—	Much degenerated	Normal ..	Fibres small
	1911 (2)	Birth	8/12	..	Non	V.H.C. fairly normal in number; slight chromatolysis	—	Not small but degenerated	—	—
	1911 (3)	? ..	3¾	..	.. .. ..	Great diminution in number and size of v.h.c.	—	Small; number of fibres diminished	—	—
Councilman and Dunn	1911	..	6/12	Yes	.. .. ..	Normal	—	—	Slight irregularity in myelination	Fibres 3 35 μ
Griffith and Spiller	1911	..	2	..	.. .. ..	V.H.C. small and scarce	Cells of xii nucleus diminished in number	Small; stained badly	Great loss of myelin in posterior tibial nerve	Atrophy of fibres; nuclei, c.t. and fat increased

of fibrous tissue. A few fibres showed internal nuclei, but longitudinal splitting of fibres could nowhere be seen.

DISCUSSION.

Professor BROUWER (Amsterdam) said he had examined one case of typical Oppenheim's disease, and in it he found the same changes in the central nervous system as Dr. Greenfield had described. He agreed there was no anatomical difference between the Werdnig-Hoffmann disease and Oppenheim's disease, but that did not prove that both diseases were the same, because when studying pathological anatomy one found only the final results of disease He considered there was a slight difference in the clinical picture in the two conditions; and in one stronger electrical currents were required to elicit responses in the muscles than in the other.

Dr. GREENFIELD, in reply, said the only point he would like to add was that in both diseases there is a striking absence of degenerative changes in the peripheral nerves and in the anterior roots, considering the rapid course of the illness. The number of cells showing acute degenerative changes is also very small. No doubt there is some clinical and quantitative difference between the two diseases, but he did not think there is any qualitative distinction.

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AMYOTONIA (*continued*).

CASES WITH AUTOPSIES.

Author	Date	Age in years at: Onset	Age in years at: Death	Improvement	Familial or non-familial	Spinal cord	Medulla	Anterior roots	Peripheral nerves	Muscles
Holmes, J. B...	1920	Birth	4/12	No	Non ..	V.H.C. diminished in size and number; some chromatolysis	—	Small ..	Normal ..	Large and small fibres; no fibrosis
Huenkens and Bell	1920	6/52	6/12	,,	1 brother aff. d. at 3/12, 1st cousin (?) aff.	V.H.C. few and small	—	—	—	Atrophy of nearly all fibres; some normal size
Slauck ..	1921	Birth	4/12	,,	Twin aff., d. at 3½, elder b. aff. d. at 4/12 younger s. aff. d. at 8/12	Diminution in number of v.h.c. with extensive degenerative changes; "empty beds"	Diminution in number of cells in xii nucleus, many showing acute degenerative changes	Degenerated	Atrophy of fibres	Simple atrophy of fibres; some fat replacement; no nuclear or c.t. increase
Michael ..	1923	1/12	6/12	—	2nd, 3rd, 4th and 5th childr. d. of same illness. Pt. 6th child	Atrophy of v.h.c. with chronic degenerative changes throughout cord, acute in lumbar region	—	Much demyelinated	Many nerves demyelinated	Normal and atrophied fibres; slight fibrosis
Greenfield and Stern	1927 1	Birth	13	—	1 brother aff.	Great diminution in number and size of v.h.c.; a few degenerated cells; "empty beds"	Great diminution in number of cells in xii nucleus	Very thin ..	Very thin; many finely myelinated fibres	Most fibres atrophied; some fibrosis and much fat replacement; internal nuclei increased
	2	,,	10/12	V. slight	1st child ..	V.H.C. greatly diminished in number and size; "ghost cells" and "empty beds"	Atrophy of xii nucleus; numerous "ghost cells"	Very thin and demyelinated	Thin; many fine fibres; fibrosis in ulnar nerve	Fibres very atrophied; none over 50 μ; some fat replacement; no internal nuclei
	3	6/12	3	Yes	No information available	Great diminution in size and number of v.h.c., a few chromatolytic cells	Acute degenerative changes in xii nucleus; loss of cells in nucleus ambiguus	Very thin: great demyelination	Thin; many fine fibres; fibrosis in ulnar nerve	Most fibres atrophied; large fibres up to 60 μ one in triceps 90 μ; some fat replacement

A CASE OF DIFFUSE MYELITIS ASSOCIATED WITH OPTIC NEURITIS.

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In 1870 Sir Clifford Allbutt [3] published a paper concerning the ophthalmoscopic signs associated with spinal cord disease. This was the first intimation of such a combination, other than that found in some of the chronic neurological diseases such as tabes dorsalis.

Nine years later a case was reported by Erb [15] of acute myelitis with optic neuritis which improved, and one by Steffan [53] in which visual disturbances were followed rapidly by a dorsal transverse myelitis. Very soon after cases of this kind were reported from England by Dreschfeld [13], and Chisholm [9]; from Germany by Rumpf (46], and Noyes [42]; from America by Seguin [50]; and from France by Chauvel [8], and Achard and Guinon [2]. Since this time a large number of cases have been published which showed a combination of neurological symptoms in which either papillitis or retrobulbar neuritis was present.

Optic changes are found in many infectious diseases, as influenza, poliomyelitis (Ghormley [24]), spinal cord tumours, cord injuries, particularly in the cervical regions (Collier and Taylor [56]), Schilder's disease (Jumentié and Valière Vialeix [32]), post-encephalitic conditions (Spiller [52], Worms and Pesme [63]), disturbances in lactation (Krausse [37]), and even in a number of apparently healthy women (Buchanan [7]). It is, therefore, difficult to state definitely that in any particular case the causes of the myelitis and of the papillitis are one and the same.

I have included only those cases in which the only, or at least the outstanding, symptoms were those of paraplegia and blindness.

I have found reports of seventy such cases. In thirty-six patients myelitis preceded ocular symptoms, and in eighteen the first symptom was the onset of blindness. In ten they came on simultaneously, while in four the neuritis was discovered only on routine ophthalmoscopic examination.

Many of the cases reported as myelitis with optic neuritis may now be confidently diagnosed as disseminated sclerosis. In others, as in that

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reported by Stewart, Greenfield and Blandy [54], the presence of symmetrical cerebral lesions seems to relate them to Schilder's encephalitis; but many cases remain in which a diffuse inflammatory myelitis was associated with a similar affection of the optic nerves, and the similarity of these cases to one another seems to establish them as belonging to a true disease entity.

These cases have been published under a variety of names—acute disseminated myelitis, diffuse myelitis with optic neuritis, neuromyélite optique aiguë, ophthalmoneuromyélite, and most recently Bouchut and Dechame have suggested "neuropticomyélite aiguë." In English literature both "diffuse" and "disseminated myelitis" have been used; the latter in some instances was meant to indicate the optic as well as the myelitic lesions. In fact, Frederick Taylor points out, in discussing Clowes' case, that perhaps the optic inflammation is but a demonstration of the possible dissemination.

In twenty-five of the recorded cases there were comprehensive pathological examinations; in nine the lesions of the cord consisted in disseminated foci, while in sixteen there was a diffuse myelitis, varying in extent from one and a half inches, to involve all the thoracic and many of both the lumbar and the cervical segments. It is possible that these two types represent two distinct diseases with a common clinical picture.

My patient was an intelligent, well-developed girl, aged 15.

On April 3, 1926—thirteen months before admission to the National Hospital—the patient was taken suddenly ill with vomiting, headache, malaise and some drowsiness. She stayed in bed a week, and then returned to school. For a month she lacked energy and had difficulty in concentrating. She recovered entirely and for a period of five or six weeks felt very well, until, at the beginning of June, she awoke one morning to find that the vision of the left eye was hazy and indistinct. This visual disturbance very rapidly got worse, so that at the end of a week she was nearly blind in this eye. The right eye became affected in the same way, and two weeks from the beginning of blindness her vision was practically lost.

She was sent to a hospital, where improvement rapidly ensued, and in a few weeks she became almost well. While in the hospital, however, she had a transient fainting attack, with a sensation of pins and needles on top of her head and in the lower part of her back.

During the next two months her health was good and her eyesight seemed to improve but then deteriorated again. About the same time she had attacks of emesis, associated with severe headache over a period of two or three weeks. She also complained of itching of the skin, loss of weight, languor and amenorrhœa. Examination showed that the pupils reacted to light and accommodation, but revealed a bitemporal hemianopia, and in the

left field, in addition, a complete inferior nasal quadrantic defect. The fundi presented the picture of secondary optic atrophy. Motor power and sensation appeared to be normal.

During this period, the patient was given intravenous injections of silver salvarsan. After the third injection, at the beginning of December, 1926, she had severe pains in her back, spreading round the left side and under the left breast. These continued for a few days, and then the lower extremities became weak and numb. The weakness of the legs rapidly progressed, in a week reaching complete paraplegia, with incontinence of both urine and fæces. All the deep reflexes were brisk and there was a bilateral Babinski response and absent abdominal reflexes. The visual fields were the same as on the previous examination, but the visual acuity was greatly reduced. After a week she rapidly improved in every way and continued to do so for two or three months, until she was, as she said, fairly well.

In April, 1927, a little less than a year after the eye symptoms had first appeared, there was a recurrence of the weakness of the legs with much subjective discomfort. This improved until the beginning of May, when again a return of these symptoms occurred, leading rapidly to complete paralysis with myoclonic jerkings and profound paræsthesiæ in both lower extremities. Blindness as well as sphincter disturbances came on and increased as the paralysis became worse. Ever since defective vision had occurred, she had seen "patterns" in front of her eyes consisting of coloured forms, usually circular, which whirled round and round. They were chiefly green, yellow and purple, and were always in motion whether the eyes are open or closed. Whenever her vision improved these patterns diminished in intensity.

On admission to the National Hospital, on May 6, 1927, under the care of Dr. Gordon Holmes, the patient was found to be alert and presented some degree of euphoria, yet she was prone to burst into tears unexpectedly and for inadequate causes. With the left eye she could only vaguely distinguish form, in the right her visual acuity was $\frac{1}{12}$. Visual fields taken with very large test objects showed large, central scotomata. There was almost complete blindness in the left temporal field and some reduction of the right superior temporal field.

Examination of the fundi by Mr. Leslie Paton showed the optic discs to be white all over, with clean-cut edges. The calibre of the vessels was not markedly decreased. The pupils were equal, and reacted well to light and accommodation. All ocular movements, except convergence, were well performed. The other cranial nerves were normal.

There were no motor or sensory changes in the arms. The abdominal muscles were feeble. The lower extremities were extremely weak, cold and cyanotic. She was unable to stand. Sensory tests showed complete analgesia and thermanæsthesia on the right side up to 3 in. below the nipple and to about the sixth thoracic vertebral spine. On the left side analgesia extended to 2 in. below the clavicle, with hyperalgesia above this level. In these analgesic areas tactile sensibility was decreased. Postural sense in the

lower extremities was partially retained. The deep reflexes were extremely brisk, and the plantar responses were extensor. No abdominal reflexes were obtainable. The spinal fluid contained only four cells per c.mm., but 15 per cent. of these were polymorphonuclear. The protein was 0·04 per cent. and the Lange reaction gave a weak luetic curve. The Wassermann reaction was negative in the blood and cerebro-spinal fluid.

In a few days severe paræsthesiæ of the hands and fingers developed, with sensory loss over the entire ulnar side of the right forearm and the posterior axillary fold. On the left arm there was a slight but definite sensory impairment of similar distribution.

A steadily and progressively ascending motor and sensory paralysis ensued during the next two weeks, associated with almost absolute blindness. On May 27, eight days before death, another lumbar puncture was performed. This gave a clear, colourless fluid, containing two small mononuclear cells per c.mm. The total protein was 0·1 per cent., Nonne-Appelt +, Pandy + +. The Lange gold curve was normal and the Wassermann reaction negative.

A few days before death, which occurred on June 4, 1927, shivering of the upper limbs developed; this gradually grew more severe as the patient approached exitus. The neck also became very rigid.

Thirty-six hours before death the patient's temperature began to fall, with a concomitant slowing of the pulse-rate. Shortly before death it was noticed that her colour had become definitely heliotrope, and the nails of the hands and feet mauve.

In summary then, this patient was well until thirteen months before death. At that time she had an illness diagnosed as "chill on the liver." Two months later her vision failed rapidly, almost to complete blindness, from which she improved. Four months later there was a return of visual loss, going on to blindness, from which she again made a good recovery. Eight months from the onset of the illness myelitic symptoms appeared, with a subsequent improvement to good health for two or three months. Once more there were visual disturbances, with slight improvement for a few weeks, and thereafter a rather rapidly ascending paralysis, blindness and death. Thus, within thirteen months she had four attacks in which either optic or paraplegic symptoms, or both, came on rapidly, reached a peak and then progressively ameliorated. Finally both groups of symptoms came on rather more slowly and progressed steadily till death.

This case is unique amongst those reported. Of these only the cases of Chauvel [8], Dreschfeld [13], Frederick Taylor [55], Bielschowsky [5], Weill and Gallavardin [60], and two of Holden's [29], showed a definite abatement or amelioration during the progress of the disease. On the other hand, the remaining seventy cases either gradually or quickly, but always more or less steadily, progressed to a certain stage, and the illness then resulted in either arrest or death. Many of the patients who survived made good recoveries, but some remained more or less stationary.

It has frequently been reported that during the progress of the disease one symptom (usually the visual disturbance) improved, or entirely cleared up before another appeared, but there invariably seemed to be a more or less constant wave of myelitic symptoms.

In the above-mentioned seven cases, except Taylor's [55], a slight or transient general improvement, lasting but for a few days at the most, was noted during the progress of the disease. In Taylor's case the disease progressed for three months, then began to improve very slightly, but the patient was taken to an infirmary where all records of her condition were lost, except that she died fourteen months after the onset of blindness. Ulrich [58] reports a case in which the right eye became blind owing to a retrobulbar neuritis, eighteen months after the left one had been similarly affected. Three and a half months later a transverse myelitis developed which resulted in death after eleven months. It is unfortunate that this extremely interesting case is recorded in but the briefest summary, and that no report of an autopsy is included.

My case, then, is the only one in which a complete record is available, which presented comparatively long periods of remission after a number of acute exacerbations.

An autopsy was done five hours after death. The body was that of a healthy-looking, well-developed girl.

The brain and cord were removed. No obvious disease was evident externally, but when the spinal cord was cut across in the fresh state areas of softening were seen throughout the thoracic region.

Considerable areas of collapse were found towards the lower parts of both lungs; they contained patches of broncho-pneumonia, some in the collapsed areas, but one fairly large focus at the right apex. There was an area of pleural adhesion overlying an area of broncho-pneumonia in the axillary portion of the lower lobe which tore out on attempting to remove the lung. The heart was healthy; the liver was congested, and microscopically showed early fatty degeneration about the portal veins. The Malpighian corpuscles of the spleen were enlarged, but this organ was otherwise normal. The left kidney was rather larger than normal, but except for congestion was healthy. The right kidney was found over the right brim of the pelvis. It was small and folded in by a capsule which appeared too small for it, so that it had a pucker down its anterior and outer surface like a coffee bean. The Fallopian tubes were somewhat congested; the ovaries were normal.

Sections taken from the posterior tibial nerve and the soleus muscle were found to be normal microscopically.

The brain, spinal cord and nerves were hardened in saline formalin; the tissue was examined by means of the usual neurological staining procedures.

THE SPINAL CORD.

Weigert-Pal sections showed continuous demyelinization from the seventh cervical segment to and including the last thoracic segment. In the seventh cervical segment the lesion was almost confined to the right column of Burdach, except at its more ventral portion where a narrow band of demyelinization extended into the right column of Goll. The cornu-commissural area was intact. The eighth cervical segment was almost identical in appearance, except

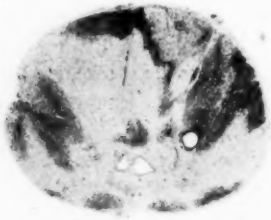

FIG. 1.—Sixth thoracic segment. A Weigert-Pal section counterstained with carmine. An area of massive demyelination, wholly unsystematized. The central canal is dilated.

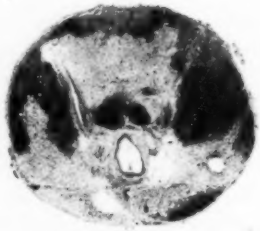

FIG. 2.—Seventh thoracic segment. A Weigert-Pal section counterstained with carmine. Less demyelination than in fig. 1. The cornu-commissural zone is less affected. The central canal is still dilated.

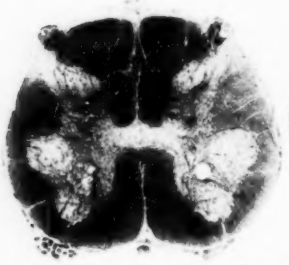

FIG. 3.—First sacral segment. A Weigert-Pal section counterstained with carmine. Although a portion of the right lateral column appears pale, the myelin sheaths are present and appear healthy.

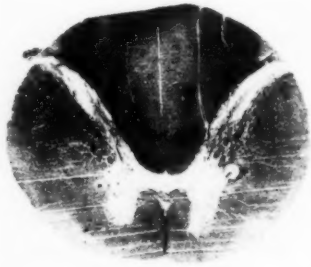

FIG. 4.—Second cervical segment. A Weigert-Pal section counterstained with carmine. Pallor of the columns of Goll and depletion of myelin sheaths in the ventral spino-cerebellar tracts.

that here the more ventral band of degeneration extended also into the left posterior column.

From the first thoracic segment to the twelfth demyelinization was massive and entirely unsystematized, except in that the cornu-commissural area was almost intact. As one examined successively lower segments of the cord, beginning with the first thoracic, normal areas of myelin seemed to melt away,

yet the outline of the degenerated areas in neighbouring segments remained very similar (figs. 1 and 2). The destruction was greatest in the fourth and fifth thoracic segments. In lower segments the normal fibres increased in number, and were particularly prominent at the periphery of the sections.

By this method of staining no descending degeneration below the area of destruction was seen (fig. 3), but above it some ascending degeneration was evident in the ventral spino-cerebellar tract and in the columns of Goll (fig. 4). In the former there was a depletion of most of the myelin sheaths, while those remaining were considerably broken up and beaded. Although the myelin appeared quite intact in the columns of Goll, it was distinctly paler than normal. Both these tracts, however, seemed unaffected from the medulla upward. The brain-stem, cerebrum, cerebellum and basal ganglia all appeared normal by this and the other staining procedures, except for the presence of some perivascular infiltration.

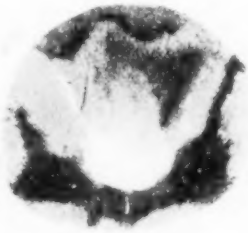

FIG. 5.—Ninth thoracic segment. A Marchi-Busch preparation. The black patches are composed of clumps of compound granule cells clustered about blood-vessels, of which there is considerable increase. Some degenerated myelin sheaths are scattered throughout the section.

The slight amount of ascending and the absence of descending degeneration are striking when one considers the enormous demyelinization, and the fact that paraplegic symptoms had been present at least five months before death. It is true that in osmic acid preparations there were some scattered degenerated fibres throughout the cord above and below the diffuse myelitis, and they were perhaps more numerous in the ascending tracts above and the descending tracts below the main disease.

The central canal was large and patent throughout the spinal cord, but at the level of the seventh thoracic segment it widened out, assuming the proportions of a real central cavitation. The cavity extended down to the eleventh thoracic segment. It was surrounded by proliferated fibrous neuroglia and ependymal cells. The columnar ependymal lining of the cavity was everywhere intact, showing it to be a congenital malformation.

Marchi-Busch preparations, particularly those counterstained by van Gieson and hæmatoxylin, were very instructive. In the thoracic region there

were large, irregularly shaped, black patches which, on examination, were found to be large clumps of compound granule cells, most of them completely filled with black-staining lipoids (fig. 5). A few degenerating myelin sheaths were present, but most had already been destroyed and had disappeared. Although granule cells were scattered throughout the sections in the degenerated area, they were much more prevalent and in greater numbers about the blood-vessels, which in the demyelinated foci had undergone marked multiplication. In sections prepared by Bielschowsky's silver method small areas of rarefaction in which even the axis-cylinders were destroyed could be seen in the thoracic segments. These lesions distinguish the pathological process of this case from that of disseminated sclerosis.

Throughout the central nervous system many vessels were surrounded by very large, perivascular cuffs of round cells (figs. 6 and 7). These were particularly numerous in the spinal cord. The vessels in the demyelinated areas were not more involved than those more remote from the main disease. The vessels of the cerebrum and cerebellum seemed least affected. The round-celled perivascular infiltration appeared to be entirely confined to the Virchow-Robin spaces. It consisted of round cells, more or less of equal size, shape and staining qualities. Intermingled with these round cells (best seen in toluidin-blue sections) were a number of plasma cells, but few if any compound granule cells, even in the thoracic region. Except in a few areas in the lumbar cord, which we shall mention later, the perivascular infiltration had not broken through the membrane limiting the Virchow-Robin space into the cord substance, although in places the cuffs distended these spaces widely. There was some exudation of round cells into the pia mater, as well as infiltration around many of the meningeal vessels.

In the first and third lumbar segments areas of exudation containing large numbers of polymorphonuclear cells were found (fig. 7). They were always centred on a vessel and associated with a certain amount of demyelinization and rarefaction of tissue and the presence of numerous enlarged neuroglial cells.

In the demyelinated areas there was a very great multiplication of the cellular elements. These cells varied greatly in size, but extremely large cells containing large, granular, centrally located nuclei predominated. The majority had a small amount of clear, pale-staining cytoplasm, but some appeared to have none. No fibrous processes were seen on these cells. Intermingled with them were a number of rod cells, particularly near blood-vessels.

Throughout the intact portions of the white matter of the spinal cord there seemed to be a slight overgrowth of fibrous neuroglia. This was particularly marked in the patches of intact myelin sheaths in the thoracic segments. Wherever the grey matter persisted the anterior horn appeared normal (fig. 7). Where it had been involved in the process of destruction the horn structure as well as the ganglion cells had all been wiped out, not even their "ghosts" remaining to show that they had once existed. The cells of Clarke's column, on the other hand, particularly in the lower thoracic region, seemed to

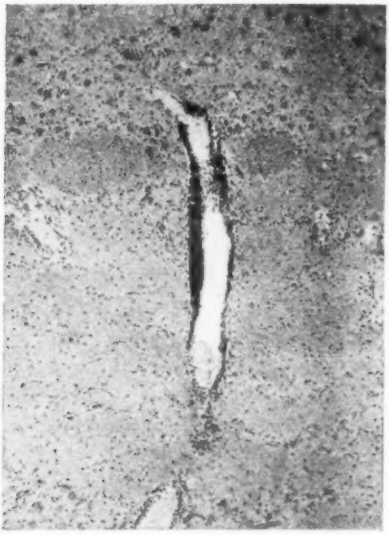

FIG. 6.—Anterior part of the hind-brain. A section stained by hæmatoxylin and van Gieson's counterstain. A longitudinally cut blood-vessel is seen with perivascular round-cell and plasma-cell infiltration.

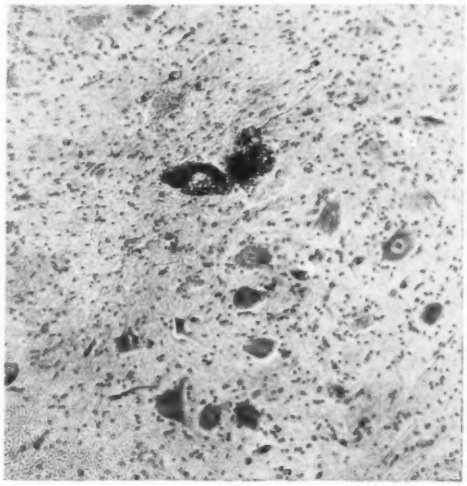

FIG. 7.—First lumbar segment stained by hæmatoxylin and van Gieson's method. Normal pyramidal cells are present. There is a vessel with marked round-cell perivascular infiltration, and above this a cellular exudate containing many polymorphonuclear leucocytes.

be undergoing some chromatolysis. By means of osmic acid impregnation and van Gieson and hæmatoxylin counterstaining, the ganglion cells were found to contain a fine, dark brown "precipitate," either scattered throughout the cell or localized to one portion of it. This "precipitate" appeared to be due to intracellular lipochrome.

This case, then, presents a massive demyelinization and smaller areas of rarefaction in which axis-cylinders were also destroyed in the thoracic and lower cervical segments, and four kinds of cellular reaction.

(1) A round-celled perivascular infiltration, always confined to the Virchow-Robin space. It is made up of round cells, a few plasma cells, and rarely gitter cells even in those localities where myelin depletion is almost absolute.

(2) In the demyelinated foci, a great multiplication of vessels which are surrounded by large numbers of compound granules.

(3) Throughout the thoracic region, an intense multiplication of cells, the greater number of which are neuroglial, but some are microglial, and many are gitter cells. There is little, if any, formation of new neuroglial fibres.

(4) In the upper lumbar segments there are some polymorphonuclear cells around the blood-vessels, associated with rarefaction of tissue demyelinization and the presence of numerous spider cells.

The Visual Apparatus.

There was a great amount of demyelinization in both optic nerves, perhaps rather greater in the right than in the left. The middle portion of the left nerve seemed to have withstood the process of destruction better than either end (figs. 8 and 9.) Here there were groups of small myelinated fibres separated by irregular areas in which the myelin sheaths had entirely disappeared, while both the anterior and posterior ends were almost devoid of myelin. The latter, however, retained some strands of intact nerve-sheaths along the periphery, which appeared to be beaded and distorted when viewed with high magnification. The right optic nerve, on the other hand, was almost demyelinated, except for a narrow band of healthy nerve-fibres along one edge.

Both nerves were extremely cellular, most of the cells being neuroglial astrocytes. Many microglial cells were found, particularly near blood-vessels. Towards the peripheral end of the right optic nerve there was a certain amount of round-cell infiltration, which ceased just posterior to the lamina cribrosa. In this nerve the perivascular infiltration was chiefly, if not entirely, composed of compound granule cells.

The more posterior portions of the optic nerves contained a number of cavities, which extended into the chiasma and also into the optic tracts. The myelin sheaths in this region had disappeared, except for a narrow rim along the periphery of the right. In these places one found an enormous cellular

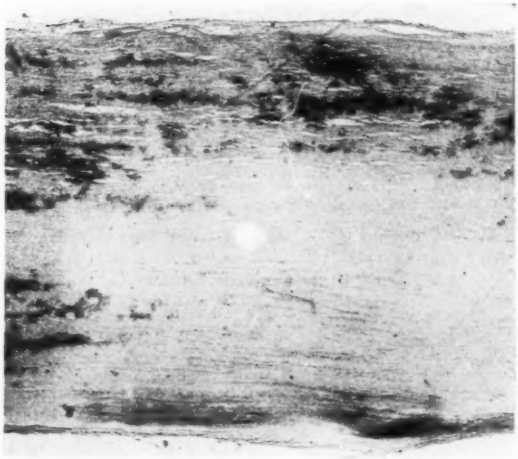

FIG. 8.—A section of the left optic nerve stained by the Weigert-Pal method. There is massive demyelination and many of the remaining myelin sheaths are distorted.

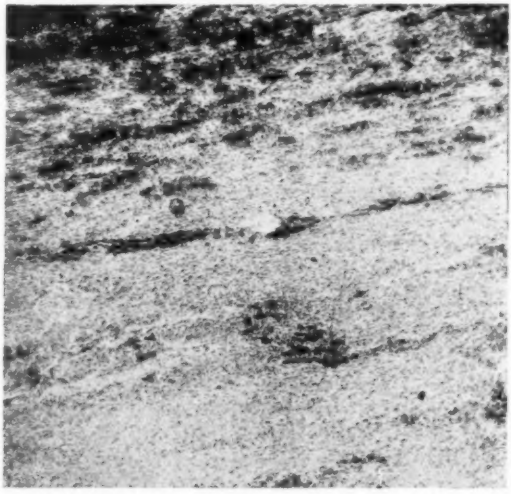

FIG. 9.—Section of the left optic nerve stained by Scharlach R. Many degenerated myelin sheaths and gitter cells are present.

multiplication. Many of the cells were neuroglial, but there were a large number of both round and compound granule cells (fig. 10).

The optic chiasma presented an unusual picture. There was some destruction of myelin sheaths in the inferior portion of the chiasma just below the tuber cinereum, while its lateral portions were almost completely demyelinated. It, too, contained many lacunæ, particularly on the left. The myelin sheaths remaining were very thin, contained many bulbous enlargements, and were rather widely spaced. There was some neuroglial cell proliferation throughout. The massive demyelination extended into the central portions of the optic tracts, extending further on the left than on the opposite side. On the right the destruction ceased just behind the chiasma. More superiorly all the myelin sheaths as well as axis cylinders had been destroyed. The commissure

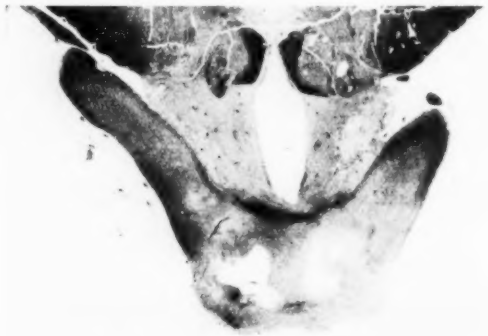

FIG. 10.—A section through the superior portion of the optic chiasma stained by Weigert-Pal's method. It contains cavities. The chiasma and part of the optic tracts are severely demyelinated. The commissure of Meynert is intact.

of Meynert, however, was everywhere intact and stained deeply. Two very large cavities had formed in the chiasma itself (fig. 10). The surrounding tissue was infiltrated with an enormous number of cells, the majority of which were compound granule corpuscles. There were also large numbers of polymorphonuclear leucocytes and many round cells (fig. 11).

The fibres of the left optic tract became increasingly paler, thinner, and more widely separated as they swung around the cerebral peduncle to enter the external geniculate ganglion (fig. 10). Most of the fibres appeared to contain irregularly arranged small bulbous swellings. In those areas in which degenerative changes were most severe there was a great increase of neuroglial cells. Many of the vessels in the neighbourhood of the optic tract as well as in that structure itself showed round-celled perivascular infiltration. In the more superior portion of the optic tract some round cell "nests" were found bearing no relationship to vessels. The lateral geniculate ganglion, superior colliculus, and the brachium of the superior colliculus were all quite normal.

Sections of the optic nerves impregnated by Bielschowsky's silver method were found to contain axis-cylinders only in the myelinated areas. The right optic nerve, in which the intact myelin sheaths were arranged at the periphery of the nerve, showed in this region a normal number of intact axis-cylinders. In the left nerve, however, the axis-cylinders in some of the myelinated areas formed a tangled network of fine fibrils; many of them had bulbous ends. It appeared to be an attempt at re-growth of axis-cylinders.

The ventral portion of the tuber cinereum where it is in relationship with the optic chiasma contained considerable perivascular round-cell infiltration associated with engorgement of the blood-vessels, and a marked cellular multiplication and infiltration. These cells consisted of compound granule corpuscles

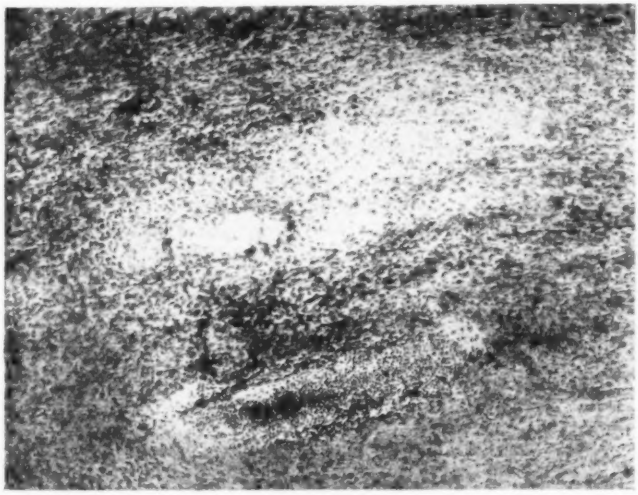

FIG. 11.—A section through the chiasma stained by Weigert-Pal's method and counterstained by carmine. A patch of softening surrounded by neuroglial and microglial overgrowth is present, with infiltration consisting of round cells, compound granule cells and polymorphonuclear leucocytes. A congested vessel surrounded by round cells is also seen.

in great numbers, neuroglial cells, particularly large ones, rod cells and many polymorphonuclear leucocytes. This inflammatory process must have involved some of the ventral nuclei of the tuber cinereum. There was a moderate amount of ependymitis in the third ventricle.

This case, then, presented symptoms of paraplegia and blindness in which there were a number of acute exacerbations and remissions. These were found to be due to a true myelitis and to an optic neuritis. The eyes were involved in each attack, but improved in each remission. The final attack terminated in a rapidly ascending paralysis.

The case was clinically unlike disseminated sclerosis. Pathologically, it differed from that disease in four main points. (1) Rarefaction going on to cavitation was found in both the spinal cord and in the optic nerves and chiasma. (2) Cell exudations containing many polymorphonuclear leucocytes were present in the lumbar regions of the spinal cord and the optic chiasma. (3) Demyelinization and destruction of the spinal cord extended continuously through fourteen segments. (4) Round-celled perivascular infiltration was found throughout the central nervous system.

On the other hand, the pathological changes bore a much closer resemblance to those found in certain cases of Schilder's encephalitis, as, for example, one reported by Stewart, Greenfield and Blandy [54]. In this case, as in that here reported, there was no sharp demarcation of the areas of demyelination, and intact myelin sheaths were frequently found in the middle of the areas (fig. 11). On the other hand, as these authors emphasized, recovery from attacks of blindness was not part of the clinical picture of that disease. Although there were close resemblances to some cases of Schilder's encephalitis, clinically as well as pathologically this case showed a number of outstanding differences. No doubt it belongs to that group of cases named by Devic "neuromyélite optique aiguë."

I wish to express my thanks to Dr. Gordon Holmes for according me the privilege of reporting this case; and to Dr. J. Godwin Greenfield for his valuable assistance in studying the pathological material.

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DISCUSSION.

Dr. GORDON HOLMES said the girl was under his care for several months. The case belonged to a well-recognized group, but the special feature was the long duration of the symptoms. At present he had under care an older patient with more or less the same symptoms, in whom the disease began with a retrobulbar neuritis and large central scotomata; only a month later she developed spinal symptoms.

These cases were not very common; he had examined three pathologically and had found the same changes Dr. Beck had now described. Some of them recovered. One, an officer from an American ship, came complaining of numbness of the legs; within a short time his legs were paralysed, and the paralysis and anæsthesia proceeded rapidly upwards until they reached the nipples. Then the man become blind in one eye, and in a few hours thereafter blind in the other. Finally the paralysis and anæsthesia ascended to the clavicles, so that breathing was carried on by the accessory muscles only. After remaining paralysed in all limbs and blind for some days, recovery set in and became so complete that within a year he was able to jump overboard and save a man's life at sea.

One interesting point was the possibility of these cases being due to some specific affection which might assume epidemic form. During 1917, Dr. Holmes saw a number of these cases in the British Expeditionary Force in France. One of them recovered from an apparently fatal condition, but several of the other cases died. It is extraordinary that, in the presence of such intense changes as those shown by Beck and others in the nervous system, so much functional recovery could occur. In that respect he considered the disease was almost unique.

Dr. C. P. SYMONDS said surely this disease was not unique, as in its capacity for recovery it resembled disseminated sclerosis. Could not the case Dr. Beck described be considered as one of acute rapidly progressing disseminated sclerosis? The distribution of the lesions was characteristic of that disease. It was true that in some respects the microscopical picture was unusual, but that was because one rarely had the opportunity of examining tissues during an acute exacerbation. None of the microscopical features which had been described were absent from a case he reported as acute disseminated sclerosis, in *Brain* in 1923.

There seemed to him no justification for regarding as a separate entity this condition, because the optic nerves happened to be involved. Surely there was hardly any toxic or infective condition of the nervous system in which there might not be either optic atrophy or papillitis.

DYSPITUITARISM OF THE LORAIN TYPE, ASSOCIATED WITH A PITUITARY CYST ARISING FROM RATHKE'S CLEFT AND SECONDARY LESIONS IN THE HYPOTHALAMIC REGION AND VENTRICLES.

BY

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In a recent address on the "Relationship of Physiology to Medicine and Surgery," Sir Edward Sharpey-Schafer [1] remarks that "the literature of the present day relating to the pituitary body is probably greater than that relating to any other subject, not even excepting the thyroid and the suprarenals . . . and although much remains to be elucidated a great deal has been discovered respecting these (its) functions, not only in connection with growth, but—as regards the posterior lobe—with the activity of involuntary muscle, with the functions of the kidney and with those of many other organs of the body."

The present-day tendency is to regard the pituitary body, together with the nuclei of the hypothalamic region, as a complex neuro-glandular mechanism rather than to adhere to the view that each lobe, anterior and posterior, is an independent endocrine organ. We venture to record in some detail the following case of "Dyspituitarism of the Lorain type," in the hope that it may help to throw additional light upon this problem, and more especially upon the relationship of the organ to growth and development. We were able to investigate the case very fully, from both the clinical and pathological standpoints; from a perusal of the literature, there appear to have been extremely few cases in which such investigation has been possible.

The patient, a girl, aged 19, first came under observation in January of this year (1927) and was shown at a meeting of the Clinical Section of the Royal Society of Medicine on February 11. She was the sixth child of a family of seven, was a full-time baby and the labour was quite normal. She had, however, always been small and weak, and was very backward up to the

age of 5. She was then treated for a year with regular doses of thyroid substance and is said to have improved greatly, both mentally and physically. Thyroid was again administered intermittently from her seventh year, but, as she was at a boarding school, the treatment was usually undertaken only during the holidays, viz., for a period of about four months in each year. Since the middle of November, 1926, attacks of headache and vomiting occurred about every three weeks, each attack lasting four or five days. She had never menstruated.

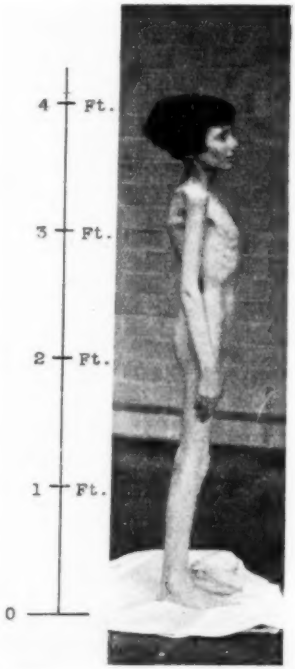

FIG. 1.—Side view of the patient; height 4 ft. 1 in., weight 47 lb.

No other member of the family is affected with any constitutional disorder, the only point of note in the family history being that the mother developed mental symptoms after the birth of the third child.

Condition on examination (January, 1927).—The patient's general appearance suggested that of a slender child, aged 6 or 7 (fig. 1). Her height was 4 ft. 1 in., and weight 47 lb. She was thin and very considerably emaciated, but the body was well proportioned, and the face, although pale and pinched, was well modelled. The head was a little large in proportion to the rest of the body. The body and limbs had lost their childish contours, subcutaneous

fat was reduced to a minimum, the breasts were undeveloped, and pubic and axillary hairs were absent. The genitalia were not large, but were in proportion to the rest of the body. The hair of the scalp was abundant and neither unusually coarse nor fine; the skin was smooth and hairless. The teeth were well developed and of relatively large size. There were only two upper incisors, and all four third molars were absent—confirmed by skiagram. All the other teeth, excepting the second lower right molar which had evidently been extracted, were present and in good condition.

According to the Stanford revision of the Binet-Simon tests, the patient's mental age was 13, and her intelligence quotient 0·7. She had an excellent memory and was quite intelligent in ordinary conversation.

The pupils were equal, central, circular, and reacted normally. The visual fields showed no abnormality, there being no bitemporal hemianopia—a point of interest in view of the post-mortem findings; the optic fundi were normal. All other cranial nerves were unaffected. The reflexes were also normal and there was no disorder of sensation nor of co-ordination. There was no enlargement of the thyroid gland.

The temperature was invariably subnormal, never reaching above 98·2° F. The pulse-rate averaged 105; the blood-pressure 110 mm. Hg systolic, and 75 mm. diastolic; the heart, lungs and abdominal viscera showed nothing of note.

Investigations.—A blood-count (December 11, 1926) was as follows:—

Blood-count: Red blood-corpuscles, 5,640,000 per c.mm.; white blood-cells, 7,200 per c.mm.; hæmoglobin (Gowers) 91 per cent.; colour index, 0·8 per cent. of unity.

Differential leucocyte count: Polymorphonuclears, 68·0 per cent.; lymphocytes (small, 20·5, large, 8·0), 28·5 per cent.; large mononuclears, 3·5 per cent.; eosinophils, 0·0 per cent.; mast cells, 0·0 per cent.; abnormal forms, 0·0 per cent. (About 0·5 per cent. of the polymorphonuclears were very "immature," i.e., verging upon intermediate myelocytes; and, as indicated above, a considerable proportion of the lymphocytes were "large," i.e., belonged to the earlier or younger cells of the series.)

The red blood-corpuscles showed a distinct diminution in their average size and a moderate degree of anisocytosis, but no poikilocytosis, nucleation, or basophilia, either punctate or diffuse. Blood-platelets were present in ordinary average numbers in the films.

The blood yielded a negative Wassermann reaction. A cerebro-spinal fluid examination on December 13, 1926, showed the presence of 267 cells per cubic millimetre; they were mostly small lymphocytes, but with about 5 per cent. of polymorphonuclears and occasional endothelial cells. Many of the cells occurred in clumps of one or two dozen, and sometimes up to 100 or more, making an actual count practically impossible. In addition to their ordinary granules, many of the polymorphonuclears and also some of the endothelial cells contained fairly large fat globules staining with Sudan III and scarlet red. Total protein 0·12 per cent.; globulin in moderate excess;

Wassermann reaction negative; colloidal gold curve resembling one of the luetic type—1234432000. The urine showed no abnormality.

Resting blood-sugar (December 17, 1926) was 0·086 mg. per cent., and a blood-sugar curve following the ingestion of 50 grm. of glucose showed that sugar tolerance was definitely raised; as the patient weighed only 47 lb., 50 grm. of glucose constituted a very large dose.

The blood-calcium content (February 14, 1927), as estimated by Collip's modification of the Kramer and Tisdall method, was 12·2 mg. per 100 c.c. of blood, the average normal amount by this method being given as 11·4 mg.

The basal metabolic rate (February 23, 1927) was minus 17 per cent.; it is doubtful if much reliance can be placed upon this result, partly on account of the abnormally small weight and also owing to the difficulty she had in breathing uniformly. Radiographic examination of the skull (December 9, 1926) revealed a sella turcica distinctly larger than normal in proportion to the rest of the skull. X-ray examination of the hands and knees also showed a wide zone of epiphyseal cartilage still unossified.

Clinical Commentary.

The clinical description of the patient, it will be agreed, corresponds with the Lorain type of infantilism, that is, a delicate undersized individual with the bodily proportions of an adult, but without secondary sexual characteristics. The first cases of human beings who for their lifetime remained in a childish state appear to have been described by Dancel and Baillarger [2], while the term "infantilism" was introduced by Lasègue. Lorain [3], in 1871, published the first exact clinical description of the type of infantilism, of which the present case is an example, but he did not associate the condition with a lesion of the pituitary body. De Sanctis [4], in 1905, appears to have been the first to attempt to explain this form of infantilism by an abnormal function on the part of the endocrine system. It was E. Levi [5], however, in 1908, who first published a case with skiagrams showing an enlarged and deformed sella turcica, due probably to the presence of a pituitary tumour. A good example, in which, additional to the presence of a pituitary tumour, the thyroid gland was absent, was reported by Lemann and Van Woort [6], in 1910, and in 1911 G. Peritz [7] recorded a case of dwarfism with congenital absence of the pituitary body. Harvey Cushing (1912) [8] described a case of the Lorain type—that of a girl, aged 18, weighing 94 lb., and with enlarged sella turcica (X-ray examination), papillœdema, and general signs of increased intracranial tension; this author considered that the condition resulted from a deficiency of function on the part of the anterior lobe. A right subtemporal decompression was performed, but the case died a

few months later, an autopsy not being obtainable. A. J. Walton [9], in 1922, recorded a similar case in which he removed the entire pituitary body; the lesion proved to be a large adenomatous and semi-calcareous cyst which lay well forward in the pituitary fossa, the anterior clinoid processes being destroyed.

A few cases of the Lorain type have been recorded (e.g., by Blair Bell [10], 1919, Parkes Weber [11], 1921), in which X-ray examination has shown the presence of, not an enlarged sella turcica, but a shallow one. It is probable that in such cases the pituitary body, or a portion of it, is either atrophied or congenitally absent. On the other hand, in those cases with an abnormally large and distorted sella, destruction of the pituitary gland, wholly or in part, has probably occurred.

Lorain characterized as "infantilism" an arrest of development which affected the mass of the individual rather than any special organ, causing delicacy and smallness of the body and a genital dystrophy. The individual, in other words, was merely an adult in small mould. Brissaud [12] objected to calling such a condition "infantilism," and agreed with Meige that the term should be restricted to an anomaly of development, in which the general morphological characters appertaining to infancy persisted in a subject who had passed the age of puberty. In 1911 Meige and Bauer [13] further elaborated this aspect, and Bauer introduced the term "chétivisme" to distinguish the infantilism of Lorain—an arrest of development with conservation of the relative adult portions of the body—from true "nanism" or infantilism, in which certain morphological characteristics of infancy were retained.

In 1911 Hastings Gilford [14] introduced the term "ateliosis" to designate a condition of "continuous youth," and it is probable that some cases have been recorded under this heading (e.g., F. Parkes Weber's cases [11]).

Clinical features which we would especially emphasize in the case described here are:—

(1) The skiagram of the skull showing a relatively enlarged sella turcica.

(2) The results of cerebro-spinal fluid examination. The cell-count of 267 cells per c.mm., mostly small lymphocytes, many of which contained fairly large, fatty globules.

When the case was demonstrated clinically at the Royal Society of Medicine, on February 11, 1927, we observed, "The clinical examination and laboratory findings indicate that some chronic inflammatory changes are taking place, probably in connection with a pituitary tumour or cyst."

Subsequent Course.

In addition to the investigations recorded above, the following tests of endocrine function were also applied to the case:—

(1) *Ascoli-Faggoli modification of the Goetsch reaction*, consisting of the intradermic injection of 0·05 c.cm. of a 1 in 1,000 solution of adrenalin chloride. A positive result, indicating some degree of hyperthyroidism, is shown by the rapid development of a dark-blue spot at the site of injection, surrounded by an increasingly intense white area, which in turn is enclosed by a red zone. The reaction was very pronounced in a case of mild Graves' disease (used as a control) but negative in our case of dyspituitarism.

(2) *Harrower's thyroid-function test* [15].—This test is based on the assumption that, if the thyroid is irritable, the administration of thyroid extract will result in an obvious rise of blood-pressure and an increase in the pulse-rate, which continues for two or more days after the ingestion of suitable quantities of thyroid preparations. If the thyroid is normal, the blood-pressure and pulse-rate are but little affected and the reaction is slight and transitory. If the gland is in a condition of "hypofunction," the stimulus of the thyroid ingested produces no reaction.

In two normal controls the reaction was negligible, but was definitely positive in a case of mild Graves' disease. In the case under observation it was entirely negative, suggesting a degree of hypothyroidism.

(3) *Harvey Cushing's thermic test.*—The body temperature can be raised in animals suffering from experimental hypopituitarism by a subcutaneous injection of 2 c.c. of a 5 per cent. solution of anterior pituitary lobe extract. Cushing has found the test of clinical value and suggests that a positive thermic reaction is an indication of deficient function on the part of the anterior lobe.

The test was carried out in the case under discussion (Armour's extract being used) on March 2, 1927, but the result was entirely negative. In two normal individuals similarly injected for purposes of control, the result was also negative, but in the case of a woman suffering from both acromegaly and tabes dorsalis a very pronounced positive reaction was obtained.

The day after the injection of anterior lobe extract (March 3), our patient developed signs of increased intracranial tension, complaining of severe frontal headache, vertigo and vomiting. Relief followed the withdrawal of 15 c.c. of cerebro-spinal fluid by the lumbar route. Compared with the cerebro-spinal fluid of December 13, 1926, the result of examination of the fluid withdrawn gave interesting results. It was colourless, and showed a very faint but distinct general turbidity (comparable to that of about a 200 million strength of staphylococcal vaccine), 642 cells per cubic millimetre were now present, together with 53 red blood-corpuscles per cubic millimetre. A differential count gave: Small lymphocytes, 50 per cent.; polymorphonuclears, 45·3 per cent.; endothelial cells, 3·6 per cent.; plasma cells, 1 per cent.

The fluid, examined soon after withdrawal and in fresh wet films stained with toluidin blue and with Pappenheim's stain, showed almost all the poly-

morphs still living, active, and unstained, only about 1 in 200 or 300 taking the stain, whilst almost all the "lymphocytes" stained strongly. Only a couple of polymorphs containing large fatty granules staining with Sudan III and scarlet red, were found in these films, but a few similar granules or globules were found free in the fluid. The results of other tests were: Total protein 0·16 per cent.; globulin in moderate excess; Wassermann reaction negative; Lange's colloidal gold curve 2345555421, i.e., an exaggerated "meningitic field" curve. Sugar, however, was still present in normal amount, and the chlorides were 0·76 per cent., i.e., *not* diminished as in ordinary meningitis.

From these findings, it was inferred that a considerable degree of irritation or inflammatory reaction had occurred, an observation which would seem to support that of Christiansen [16], who attributed the excess of cells found in pituitary and suprapituitary tumour to subacute meningitis following erosion of the base of the sella turcica by pressure. On the other hand, the inflammatory reaction might have been caused by the rupture of a pituitary or a suprasellar cyst and the consequent diffusion of its contents, especially cholesterol, a suspicion confirmed eleven days later by the post-mortem findings.

Within a short time of the temporary relief afforded by the lumbar puncture of March 3, the patient again relapsed, vomiting increased, she became progressively more drowsy and died on March 14, 1927. This fatal termination was probably caused or hastened by rupture of the cystic tumour as found at autopsy.

Summary of Post-mortem Findings.

Autopsy twelve hours after death. The external appearances have already and sufficiently been described. Subcutaneous fat was present only in minimal amount, and there was also extremely little extraperitoneal and omental fat.

Head.—The bones in the cranial vault were distinctly thin, but fairly dense, consisting chiefly of outer and inner tables with very little diploë between them. The sutures, including the interfrontal, showed no synostosis, but there was complete interlocking and the fontanelles were completely closed. The cerebral membranes revealed no obvious abnormality. They were very closely in contact with the subjacent markedly flattened convolutions, which were very "dry" and somewhat sticky, and to which they clung slightly, there being no visible trace of cerebro-spinal fluid between them, and no naked-eye evidence of any surface meningitic exudate. The surface vessels in the sulci were only slightly congested, and the general colour of the brain was pale.

The brain weighed 1,195 grm.; and on removing it a firm, partially calcified, and somewhat nodulated, projecting mass (see figs. 2 and 3) was found in the position of the pituitary body, its stalk and the infundibulum. The lower part of this was still in position in the distinctly enlarged sella; from between the posterior wall of the sella and the tumour there welled out some 2 or 3 c.c. of pale yellowish to slightly pinkish-yellow, thick, slimy, necrotic-looking fluid, suggesting the contents of a ruptured cyst, the ragged

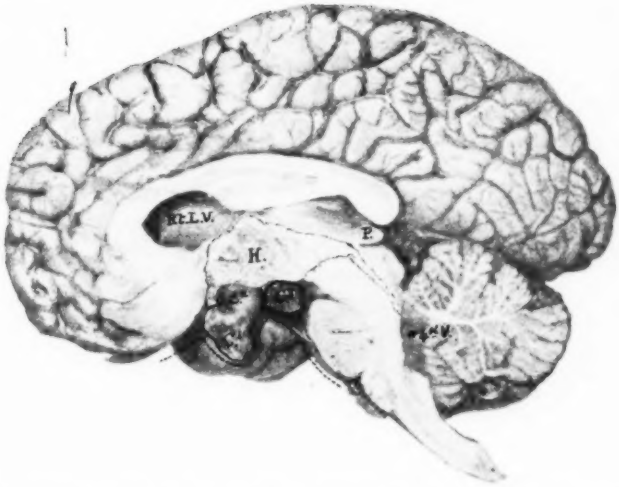

FIG. 2.—Vertical-mesial section of brain, showing mesial surface of right hemisphere. Dotted line indicates outline of sella. C^1., intrasellar cyst. C^2., suprasellar cyst, both partially calcified. C^3., thin-walled cyst containing débris, cholesterol crystals, &c. H., tumour in region of third ventricle and hypothalamus. P., pineal gland. Rt. L. V., dilated right lateral ventricle. *4th V., fourth ventricle, showing "granularity" of wall ("ependymomatosis?").

FIG. 3.—Radiogram of the pituitary and brain tumour replaced in the sella turcica to show the very important supra- and intra-sellar calcification, a point in diagnosis emphasized by Cushing and his collaborators. (Dr. Martin Berry.)

and irregular wall of which could be seen as a concavity on the posterior aspect of the projecting mass; whilst, still adherent to the posterior wall of the sella, was another rather soft portion of the cyst wall, which was removed for microscopical examination, and in which only a minute islet of surviving pituitary tissue was found. The fluid contained a few cholesterol crystals, fatty globules, and debris; also numerous cells, including polymorphs, vacuolated (i.e., fat-droplet containing) endothelial-like mononuclears, smaller lymphocyte-like cells, an occasional cell still showing cilia, and numerous red blood-corpuscles. No micro-organisms were detected. The sella measured 16 mm. antero-posteriorly, and was 19 mm. wide and 12 mm. deep. The posterior wall of the sella was still largely cartilaginous, and the cartilaginous junction of the basi-sphenoid and occipital bones was of considerable width (bony ankylosis between these normally takes place about the twenty-fifth year). The optic chiasma was covered over and buried by the suprasellar part of the pituitary mass, and the optic nerves emerged on each side of it. The chiasma looked as if it might have been compressed, though a careful examination during life had not elicited the presence of a bitemporal hemianopia. A second thin-walled cyst (fig. 2, C^3) about the size of a kernel of a small hazelnut ($11\frac{1}{2}$ mm. in antero-posterior diameter) was present above the dorsum sellæ over the posterior perforated spot, between the upper or suprasellar part of the foregoing and the antero-superior margin of the pons. This had a thin fibrous-tissue wall, and contained dark-red necrotic-looking contents, amongst which numerous minute glistening scales of cholesterol could be seen. The suprasellar portion of the first described mass (fig. 2, C^2) was pale-brownish in colour, and showed extensive calcification; whilst above it, in the region of the third ventricle and hypothalamus, there was an extensive infiltrating mass of tumour (fig. 2, H) extending upwards to the under surface of the fornix and to the walls of the bodies of the lateral ventricles. This was found microscopically to extend to the base of the pineal gland (fig. 2, P) and along the aqueduct of Sylvius.

The ruptured cyst, which had obviously occupied the sella, showed microscopically a wall varying very much in structure at different parts—a mixture of old fully-formed fibrous tissue, and recent subacute granulation tissue, both containing patches of cholesterol "clefts" (fig. 4); also at one point, pressed up against the posterior wall of the sella, was a minute islet of degenerating anterior gland tissue, with, possibly, a very minute fragment of posterior lobe beside it (see fig. 5) was found. This cyst was lined with ciliated epithelium, evidently originally in a single layer of tall columnar cells (figs. 6 and 7), but at parts now much altered and undergoing a chronic irritative proliferative change, forming here and there multinucleated plasmodial masses and occasional little papillary ingrowths. Many of these ciliated cells, single or in clumps, had been cast off into the cyst cavity (fig. 7), whilst others had been displaced outwards into the granulation-tissue, had formed plasmodia-giant-cells and irregular islets, and possibly given rise to the infiltrating suprasellar tumour—though one cannot, perhaps, exclude the possibility that this

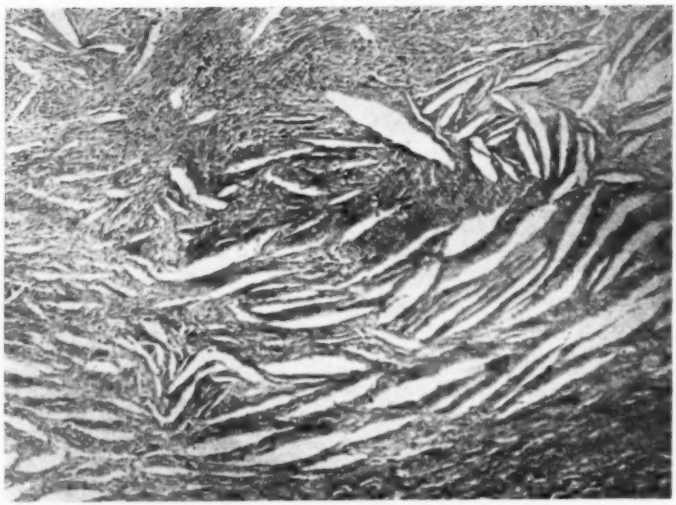

FIG. 4.—Section of old fibrous tissue portion of cyst wall, showing cholesterol clefts, around which giant cells are not in evidence. (Low power.)

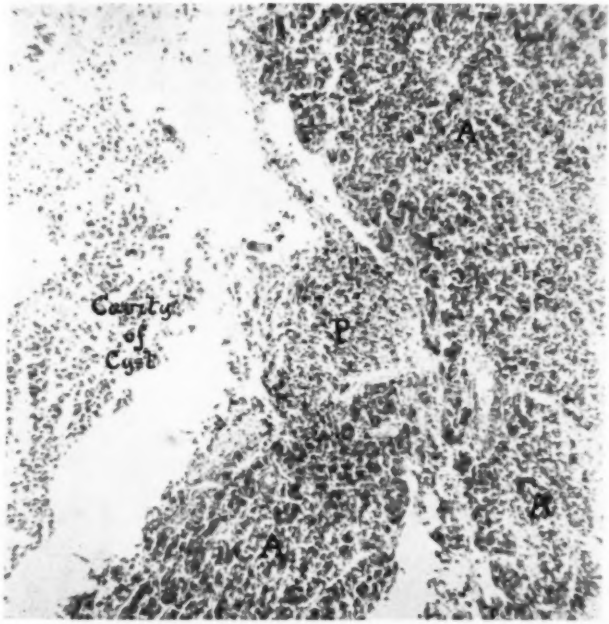

FIG. 5.—Section of cyst wall adherent to the posterior wall of sella. Small islet of surviving, but degenerated, pituitary-gland tissue. A, A, A, anterior lobe, in which both eosinophil and basophil granular and non-granular chromophobe cells are still distinguishable. P, minute islet of posterior lobe. (Low power.)

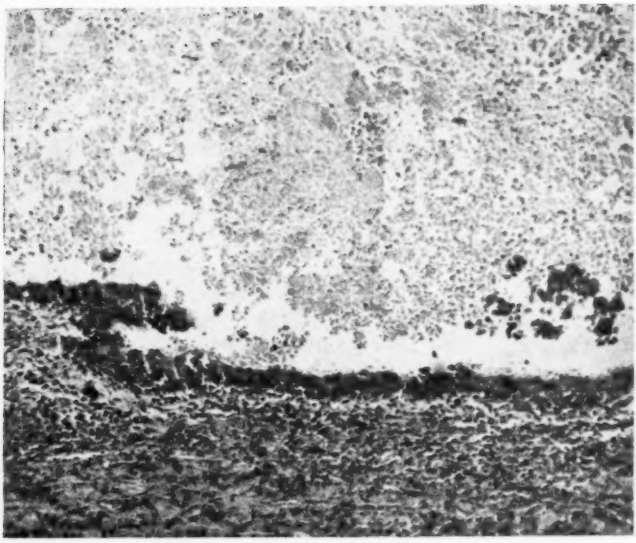

Fig. 6.—Portion of wall of intrasellar cyst, showing lining of ciliated epithelial cells. (Low power.)

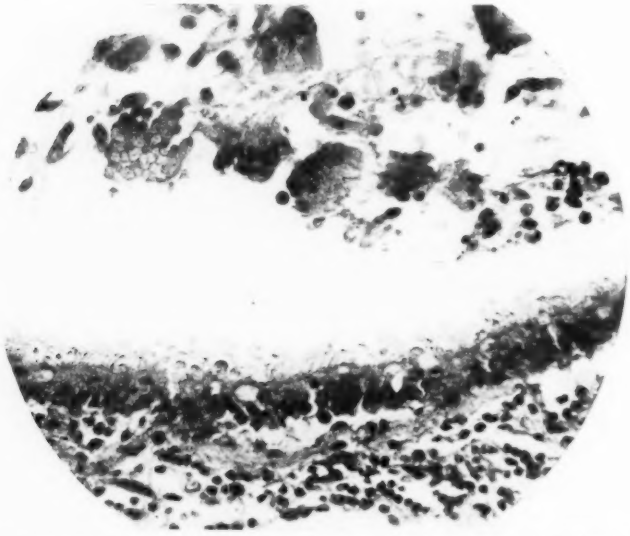

FIG. 7.—Portion of the wall of the intrasellar cyst, showing irregular proliferation of the ciliated epithelial cells, masses of which have been cast off into the lumen of the cyst. (High power.)

may have arisen independently from the ependyma of the third ventricle. There was moderate, but distinct, dilatation of the lateral and fourth ventricles, the walls of which showed a fine granulation-like roughening, due to chronic irritative proliferation of the ependymal lining, perhaps of the same nature as the "ependymomatosis" referred to by Spiller in the discussion at the end of Percival Bailey's paper [17] upon Ependymal Tumours.

The tumour in the region of the third ventricle and hypothalamus (see figs. 2 and 8), when newly cut after fixation of the brain in formalin, had a more or less solid appearance. Later, however, owing to shrinkage, it showed as a sponge-like series of cysts, with semi-solid contents and intervening granulation tissue, at some parts chronic, at others more subacute and cellular. The lining cells of these cysts (figs. 8 and 9) were arranged in a somewhat indefinite and ragged row, at some parts single, at others proliferating in masses. These cells closely resembled those found lining the ventricles, aqueduct of Sylvius, and fourth ventricle; and it is possible that they may have been derived from the ependymal lining of the third ventricle.

Other points of interest in the naked-eye and histological post-mortem findings were the extremely rudimentary condition of the uterus, the walls of which varied from only 1·5 to 2 mm. in thickness, muscular tissue being practically absent, and the cavity lined by a single layer of epithelium. The ovaries were like those of a young child, measuring respectively 33 and 35 mm. long, by 10 mm. broad, and 4 mm. thick. They contained both primitive and partially ripening ovarian follicles; but, at all events in the portions cut, they showed no definitely developed corpora lutea.

The *pineal* gland was of moderate size (fig. 2, P), apparently normal in structure, with only a few small calcareous areas in it. The *thyroid* (1·8 grm.), *thymus*, and *suprarenals* (right 1·3, left 1·2 grm.) were all small in size, their histology suggesting only moderate, or diminished, activity.

The histological examination of the other organs and tissues has brought out nothing of obvious importance, excepting that there was a distinct leucoblastic reaction in the bone-marrow.

The weight of the different viscera was as follows: Total body weight, 21·08 kg.; brain, 1,195 grm.; heart, 80 grm.; lung, right, 130 grm.; lung, left, 115 grm.; liver and gall-bladder, 500 grm.; spleen, 47 grm.; kidney, right, 47 grm.; kidney, left, 50 grm.

The tumour, therefore, appears to be a ciliated epithelial cyst, derived from Rathke's cleft or pouch, or a diverticulum of it. The intrasellar and oldest portion of the lesion consists of this cyst which has ruptured; the suprasellar portion shows extensive calcification; and both contain numerous patches of cholesterol crystals. The region of the third ventricle and hypothalamus is invaded or replaced by a sponge-like series of cysts, surrounded by chronic and subacute inflammatory reaction. There is also an "ependymomatosis" of the lateral

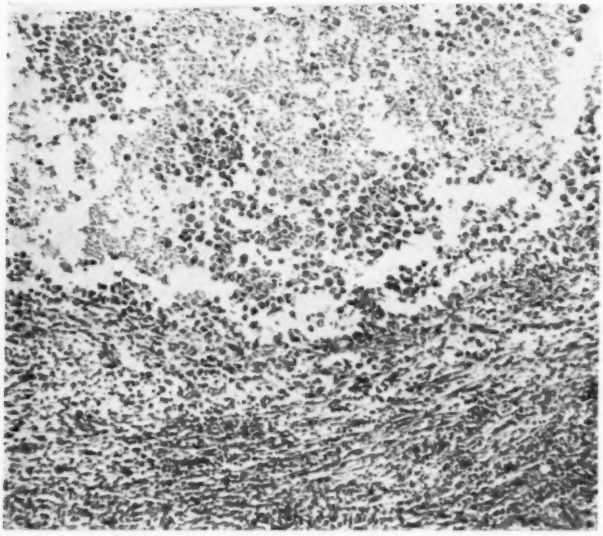

FIG. 8.—Hypothalamic portion of tumour, showing wall of one of the smaller cysts, lined by (?) proliferated ependymal cells from third ventricle. (Low power.)

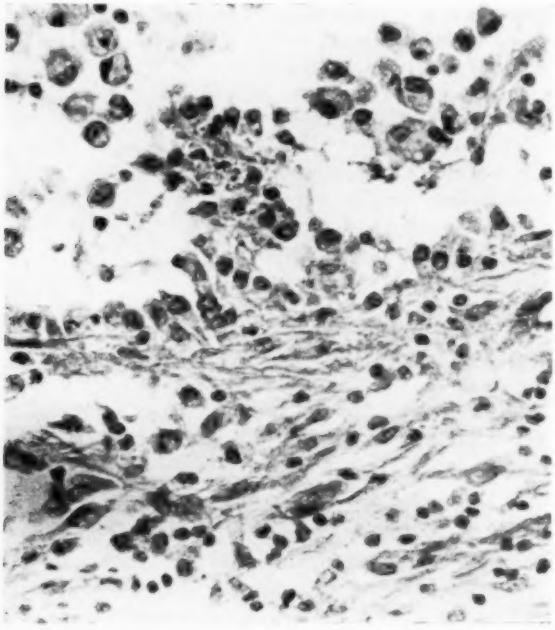

FIG. 9.—Hypothalamic portion of the tumour, showing (?) ependymal cells. (High power.)

ventricles, aqueduct of Sylvius, and fourth ventricle, which may be of the nature either of a neoplastic formation or a chronic irritative proliferation.

Physiological Observations.

Recent research has indicated that many symptoms formerly ascribed to a lesion of the pituitary body itself may result from lesions involving the closely related hypothalamic region of the brain. Karpus and Kreidl first showed that under experimental conditions certain hypothalamic centres could affect the sympathetic nervous system. Following this, Camus and Roussy [18] were able to produce typical dyspituitary syndromes in dogs by injury to the tuber cinereum above the pituitary gland, the latter being left intact. Similar results were obtained by Aschner, Hanchett, and others in America, and by Bailey and Bremer [19] in Belgium. These observations raised considerable doubt as to a lesion of the pituitary body itself being responsible for the symptoms usually ascribed to hypopituitarism, and indicated, as suggested by Erdheim, that a disturbance of the hypothalamus was the cause of many of the symptoms attributed to pituitary derangement. Also, several clinical cases have been reported in which diabetes insipidus, glycosuria, adiposity, and even Fröhlich's dystrophia adiposogenitalis, have been observed in association with lesions of the hypothalamus. In some of these cases histological examination of the pituitary body has shown no visible abnormality. Further, there is evidence, both clinical and experimental, that the hypothalamus is also concerned in the regulation of temperature and the control of sleep.

The evidence at present available, therefore, strongly indicates the pituitary endocrine organ as a complex neuro-glandular mechanism, consisting of a pars anterior, pars nervosa—and probably also pars tuberosa and intermedia—together with the nuclei of the hypothalamic region of the brain. The latter nuclei would appear to control, as it were, the function of the different pituitary lobes. Consequently, a disturbance of the hypothalamic region would be just as likely to produce symptoms of dyspituitarism as would a lesion of the pituitary gland itself.

In certain cases following encephalitis lethargica, dyspituitary syndromes—excessive adiposity, increased carbohydrate tolerance, genital dystrophy—are sometimes observed. The pathological evidence that the pituitary gland is ever involved in encephalitis lethargica is very slender. A few cases have been recorded in which minute hæmorrhages

have been found in the organ, but the lesions appear to have been too slight to produce any serious degree of functional disturbance. On the other hand, with the well-known predilection of the virus of encephalitis lethargica to involve the grey matter of the brain, the nuclei of the hypothalamus might well be involved, and, if they act as controlling centres of pituitary function, such involvement accounts for the dyspituitary syndromes met with following this disease.

In the case we have described it is evident that if the pituitary body possessed any functional activity at all it must have been excessively slight. Of both anterior and posterior lobes only minute remnants were discovered on histological examination. Similarly with the hypothalamic region of the brain; whatever function it possessed must have been seriously interfered with owing to its invasion by the cystic tumour.

The presence of a lesion that must have involved the whole of the alleged pituitary mechanism—nervous and glandular—resulting in the Lorain type of so-called hypopituitarism, almost suggests that this condition is in reality "*a*pituitarism"—or absence of pituitary function—whilst the Frölich type of hypopituitarism, due to a partial lesion of the pituitary mechanism, might well be "*dys*pituitarism," or merely disordered pituitary function on the side of diminished activity.

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CLINICAL MEETING.

A Case of Subdural Blood-cyst in Right Frontal Region located by Pneumo-radiograms.

By Sir JAMES PURVES-STEWART, M.D.

R. M. W., male, aged 18. At the age of 12 he had cerebral concussion following a fall on the ice. Four months ago he developed headache and diplopia. There was no diminution of visual acuity, but the optic discs were slightly blurred. The only other abnormal sign detected was paresis of the right external rectus and of the left side of his face. There was no sensory or motor abnormality in the limbs, and the reflexes, both deep and superficial, were normal and symmetrical on the two sides. The cerebro-spinal fluid contained six lymphocytes per c.mm., albumin was 0·02 per cent., glucose 0·05 per cent., the gold curve was normal, and the Wassermann reaction negative.

The optic discs became progressively swollen to + 4·5 D in the right eye and + 2·5 D in the left eye. Visual acuity and the visual fields remained normal, but the blind spot in both eyes was slightly enlarged. Pneumo-radiograms showed displacement of the right lateral ventricle towards the left side.

In view of these findings, a wide decompression was carried out in the right frontal region. The subjacent dura was tense, and on being incised a subdural cyst, about the size of a turkey's egg and containing black altered blood, was evacuated. The subjacent cortex was then seen to be normal, save for brownish pigmentation of the pia arachnoid.

Clinical improvement since operation has been uneventful. The swelling of the optic discs subsided rapidly, and there is now only a faint trace of left facial paresis. The bony gap on the cranium is concave.

Last month I saw a second similar case in a man who had had signs of Jacksonian epilepsy, with deviation of his head and eyes towards the right side. A cortical lesion was diagnosed, and to confirm the diagnosis pneumo-radiography was employed: it showed that both lateral ventricles were displaced to the right side. The man died unexpectedly and suddenly a short time afterwards, and on post-mortem examination a cyst, as in this boy, was found in the left pre-frontal region, displacing both ventricles to the other side.

Dr. PETRÉN (Lund) said he had seen many cases in which pneumo-radiograms enabled the localization of a cerebral tumour to be made, but this was the first instance he had seen in which it revealed the presence of a blood-cyst, and formed a guide to such successful treatment.

A Case of Falling on Noise and Surprise.

By GORDON HOLMES, M.D.

D. D., aged 14, comes from healthy stock in which there is no history of any affection similar to that with which he suffers. Both parents and most of his other relatives are large-boned and tall. There is no epilepsy or psychopathic taint in the family.

He has always enjoyed good health. At the age of 2½ years he had scarlet fever and increased in weight since then. He is intelligent and has done exceptionally well at school.

At the age of 5 it was noticed that he was liable to fall, often without any apparent cause, but usually on hearing a noise. This tendency to fall became more pronounced when he was about 8 or 9, and since then any loud sound, as a tyre bursting, a motor hooting, a door slamming, a rifle shot, &c., may bring about a fall. Less frequently a surprise, as coming into a room which he had expected to find empty, being overtaken silently by a cyclist, a wasp or a butterfly flying suddenly in through the window, a cat jumping on to a table, or being touched from behind, may bring about a fall.

The element of surprise is, however, not essential; he has frequently fallen, for instance, on hearing a gas fire which he was watching being turned off, go "pop." In falling he has fractured his limbs repeatedly.

The falls are not preceded by any warning, and from his own account there is never any degree of loss or disturbance of consciousness; this has been confirmed repeatedly by observation. There is no change of colour, and no vertigo or giddiness. His limbs suddenly flex under him and he falls flaccidly to the ground. He has lately noticed his left leg weak for about thirty seconds after certain falls, but he can generally rise at once without any assistance.

He has been treated with thyroid, pituitary and other organic extracts, and lately by bromide and luminal, without any benefit.

He is unusually tall for his age and is unnaturally fat, probably because he plays no games and takes little exercise. His skin is soft and rather hairless; hair distribution is still of the adolescent type, but his genital organs are well developed. Radiograms of his skull reveal a rather small sella turcica. His visceral organs and urine are normal; his systolic blood-pressure is 120 and the diastolic 80. The blood-sugar curve shows a slight delay in descent.

There is no evidence of organic nervous disease; his reflexes, optic discs and visual fields are normal.

While he was in hospital he had an epileptic attack at 4.40 a.m. on June 6, 1927. The onset was sudden during sleep; he became blue, his limbs were convulsed and his eyes deviated to the right. He did not lose sphincter control or bite his tongue. He now admits that he has occasionally on previous occasions noticed a soreness of his tongue on waking in the morning.

Although it was generally easy to produce a fall by a sudden noise while the patient was in the wards of the hospital, it was not possible to demonstrate this symptom before the Meeting, probably owing to the patient expecting the experiment to be made and being consequently on his guard.

Dr. W. J. ADIE (London) said that for some years he had been particularly interested in sudden attacks of all kinds, and he had read accounts of many queer conditions, but nothing like the symptoms of this case. He did not think this boy's condition was related to narcolepsy, as in this disease the patient falls to the ground slowly after some emotion, laughter being the most potent. Or he may fall if he becomes angry or annoyed, but never, as far as he knew, on hearing a loud noise, or on receiving any sort of shock. On the other hand the boy presented never fell when he laughed, nor had he attacks of inevitable sleep, as nearly all cases of narcolepsy.

Myotonia, or Thomsen's disease, is another cause for falling like a log, as this boy did. In 1837 Charles Bell first described this condition; some years later Thomsen recognized it, and mentioned that his patient "fell like a log." Dr. Rosett has also described admirably a number of patients with myotonia, whose only symptom was that they fell when surprised or emotionally disturbed. The myotonic, however, fell stiffly, whereas this boy's limbs were lax when he collapsed.

He thought the family history of this case should be investigated, to determine if relatives suffered with myotonia. His own view was that this case belonged to a class by itself. The *Lärm-Epilepsie* of the Germans is different, for patients subject to it had epileptic attacks on hearing a loud noise, and that was not so in the boy.

Dr. WEISENBURG (Philadelphia) said that a feature in this case which interested him was the ability of the patient to arrest falling under certain circumstances. Years ago, when he was making a study of emotional expression by moving pictures, he collected a number of patients from psychiatric wards who howled almost continuously, two of them making such a noise that they kept the other patients awake. He took them to the moving-picture studio in the hope that they would howl, but they did not, though other onlookers often cried at emotional pictures. Neither would they laugh, though attempts to make them do so were kept up for two hours. When the observation was concluded and the camera was taken away, the patients promptly started to howl again.

He had also collected a group of epileptics who were subject to several fits daily, but when they were placed in front of the camera the first day passed without a single patient having a seizure. But on the following morning, when the novelty had worn off, fits began to occur. The lesson was that these so-called involuntary phenomena were not really involuntary, or could at least be checked by voluntary effort. The probable reason that this patient did not fall while being demonstrated, was that his attention was directed to the possibility that he might fall.

Dr. MUSKEN (Amsterdam) thought this case should be regarded as one of myoclonic epilepsy. Children suffering with this condition had a tendency to fall, and often a movement of the head to an unexpected noise was actually sufficient to bring them down.

Dr. M. CRITCHLEY (London) said that he had had many opportunities of

examining the boy, and had found that in order for falling to occur the causal noise must be unexpected, as being aware of the likelihood of a noise put him on his guard. If during temporary distraction of attention a noise was made the patient fell. He had not seen myoclonic jerks in this patient. On several occasions he had tested the tone of the muscles of the patient while he was on the floor, but had found no alteration of tone, nor abolition of the tendon-jerks.

Dr. C. P. SYMONDS (London) said that some years ago he saw a case which presented somewhat similar symptoms to this present patient, but which could be more properly grouped under "auditory epilepsy." That young man had local epileptic attacks, with falling and loss of consciousness, whenever he heard a band or any musical instrument. Dr. Foster Kennedy had written on this group. Cases of a similar nature had also been recorded in Germany. He thought the present case was a variant of epilepsy, for the boy, besides falling, had one definite epileptic attack. Further, sometimes epileptic attacks occur without the patient losing consciousness.

Dr. CHARLES DANA (New York) said that some years ago he observed a number of cases resembling that now presented here, i.e., patients who fell without having definite convulsive movements. One typical attack was seen in the hospital in which the patient fell flaccidly. He felt sure that these cases, as well as the boy presented, belonged to the epileptic group.

Dr. GORDON HOLMES, in reply, said a leucocyte count in this case was done as a matter of routine, but revealed nothing abnormal.

When he first saw the boy he recalled the group of cases described by Rosett, but there was no history of myotonia, or any related symptoms in this boy or his relatives. The present was the only occasion he had known in which the patient did not fall in the presence of a sudden noise. It must have been due to the unusual circumstances, the boy being probably keyed up to expect something to happen, so that the noise did not take him unawares. The boy was very nervous about falling, and he disliked being subjected to the test. He did not think the patient presented symptoms to justify the diagnosis of myoclonic epilepsy.

Myasthenia Gravis in a Boy aged 10.

By W. J. ADIE, M.D.

D. B., male, aged 10.—Rapid onset, two months ago, of double vision and generalized weakness of all movements, most severe in the distribution of the cranial nerves. He now has a paresis of all voluntary movements, most obvious in those of the face, eyes, jaw and neck, limited ocular movements, bilateral ptosis and slurred speech. There is no muscular wasting or fibrillation. The electrical reactions are normal in all muscles and the myasthenic reaction has not been obtained. The tendon responses are all much diminished and the plantar responses are plantar-flexor. There is no evidence of enlargement of the thymus on X-ray examination.

Sir JAMES PURVES-STEWART (London) asked whether Dr. Adie had examined the microscopical structure of the muscles, and if so whether he had been able to find a patch of lymphocytosis. If not it seemed to him possible that the condition might be the result of an attack of encephalitis lethargica.

Dr. FEILING (London) said he has observed symptomatic myasthenia gravis following encephalitis lethargica. A female patient, whom he had under observation for three years, developed in 1921 encephalitis lethargica. He first saw her about two years after the original illness, and then she presented well-marked ophthalmoplegia in both eyes, but the remarkable feature was the varying of these ocular palsies. At first there was a complete ptosis and an internal squint of the right eye, and a weakness of the left external rectus. A week or two later he was surprised to find ptosis on the left side only. The ocular palsies varied in this way till last year, when they became more or less permanent.

Dr. T. DILLER (Pittsburg) agreed with the diagnosis of myasthenia gravis in this case. The disease had always interested him, as it is one of the few diseases in which consciousness is preserved until the moment of death.

Dr. H. H. HOPPE (Cincinnati) also regarded the case as a typical one of myasthenia gravis. He had never seen the symptoms-complex of myasthenia gravis following an attack of encephalitis.

Dr. ADIE, in reply, said he was interested in the account of Dr. Feiling's case, but it did not, to him, simulate one of myasthenia closely enough to raise any doubt of its diagnosis. He could confirm Dr. Diller's description of sudden and occasionally unexpected death in myasthenia gravis.

A Case of Familial Periodic Paralysis.

By W. J. ADIE, M.D.

R. B., male, aged 13.—During the past four years he has frequently waked up during the night or early morning to find that he cannot stir his arms or legs, or speak. These attacks are unassociated with any regularly occurring previous event or experience. The weakness is maximal at its onset and passes off gradually—sometimes in three or four hours, sometimes not completely for two days. During the height of the attack he cannot speak or swallow, and lies supine without any tendon reflexes. The plantar responses are always flexor. These attacks occur on the average once each fortnight.

His father had suffered from exactly similar attacks since the age of four, and they are more severe and more frequent than those of his son.

Dr. DILLER (Pittsburg) said he wondered how many members recalled that one of the earliest contributions to the subject of family periodic paralysis was made by Dr. George Holtzapple, of New York. He was a practising physician, and his skilful observation and the number of cases he quoted made the paper still the most notable on the subject.

Congenital Deformity or Old Injury to Cervical Spine, with a Recent Onset of Paraplegia.

By W. J. ADIE, M.D.

G. H., male, aged 36, a labourer, has suffered with epilepsy since the age of 14. His left arm was always smaller and weaker than the right. In his last fit he fell heavily on the back of his head; since this accident, whenever he hyper-extends his neck a feeling of painful tingling passes down his body to his feet.

Present condition.—Gross deformity of spine in lower cervical and upper dorsal regions: fine nystagmus, bilateral ptosis, mild spastic paraplegia with extensor response on both sides, patchy analgesia over trunk and lower extremities and occasional incontinence of urine. He has also pterygium, accessory auricles, inguinal hernia and a fibroid lung on the left side.

Dr. E. SACHS (St. Louis) asked whether the X-ray pictures were taken through the open mouth, with a view of determining whether there was a fracture of the odontoid process. Several years ago he saw a woman who was riding in a taxi-cab when the driver went over an inequality in the road; she was thrown out, her head striking the top of the cab. She immediately felt a peculiar tingling sensation down both arms. By the time she got home she was able to get out of the cab, and was apparently well. Her brother, who was a physician, when he heard the story he had a skiagram taken, and the report of the radiographer was that it revealed no fracture. Two weeks later she consulted the speaker, and though nothing abnormal was evident on physical examination, when she tilted her head back she had pain. As he had seen this occur in a previous case, he suggested that she probably had fracture of the odontoid. A second skiagram taken through the open mouth showed a fracture of the odontoid process without any displacement. She did not develop any further symptoms.

Mr. GEOFFREY JEFFERSON (Manchester) said he had never seen symptoms similar to those in this case result from a fracture, and he did not think that the man's present symptoms were the result of an injury. The junction of the cervical and thoracic vertebral was almost the rarest point of the spine at which fracture took place. His view of the condition shown in the radiograms was that it is a congenital abnormality of the vertebræ.

Dr. ADIE, in reply, said he did not know how the skiagram of the spine was taken. He was glad to hear Mr. Jefferson agree that it was a congenital deformity; he thought it was related to Sprengel's deformity, but the case in other particulars does not resemble this condition.

A Case of Involuntary Movements probably allied to Torsian Spasm.

By Dr. PURDON MARTIN.

M. O., a male, aged 46. In 1916, while serving in the Navy, he was "blown up" when his ship was torpedoed. He was subsequently treated at a naval hospital because of an injury to his left hand, and when the injury had

healed he was discharged from the Navy. The reason for his discharge is not known, but very soon afterwards he became aware of involuntary movements in the right arm.

Present state.—Convulsive rotation and extension movements of the right arm, with rotation of the head to the left. The degree and extent of movement is variable. When it is most severe the trunk is turned towards the left and flexed to the right, so that the right shoulder comes downwards and forwards. At times bilateral convulsive contractions of the abdominal muscles occur, jerking the upper part of the body forward. Grimacing is frequent.

If the patient wishes to smoke a cigarette when the movements are pronounced, he abandons the use of his hands altogether and lays the lighted cigarette on a table in a cigarette holder; he then rotates his head to the left, brings it down to the table, and in the intervals between the involuntary movements manages to grasp the end of the holder between his lips.

There is no loss of power, of superficial sensation, or of sense of position. Postural tone is not appreciably altered in any of the limbs. The tendon-jerks are brisk and the plantar reflexes flexor. There is no nystagmus and all the ocular and pupillary movements are normal.

Dr. CHARLES DANA (New York) said that some years ago there was presented to the American Neurological Association a case with continual contractions of the muscles of the pelvis, which twisted the patient to one side. In other cases involuntary movements, resembling those of torticollis, may involve the lower extremities. The disease may therefore affect various regions of the body. Dr. Purdon Martin suggested that the torsion spasms were of the same order as torticollis, and the speaker thought that was correct.

Dr. ALFRED TAYLOR (New York) said he had seen a case of this type in which chiefly the right shoulder muscles were involved; if the patient used a sling or rest for the elbow, or rested the arm on a chair, the torsion movements almost disappeared. There was well-marked osteitis around the fifth and sixth intervertebral foramina, and treatment by endothermy caused a considerable improvement in the spasms by the end of two months. Treatment was still being continued; it was not certain yet whether a complete recovery would be effected.

Dr. RUSSELL BRAIN (London) said he was much interested in the character of the movements in this case; extension of the elbow, associated with internal rotation and pronation of the forearm, was constantly repeated. This is the attitude which Dr. Kinnier Wilson first described as being the posture of physiological decerebration in man, and he consequently thought these cases should be regarded as due to an intermittent discharge from centres, the unchecked activity of which determines the picture of human decerebration.

Dr. PURDON MARTIN, in reply, said he agreed with Dr. Dana's remarks He was, however, unable to accept Dr. Brain's suggestion; in his opinion our knowledge of the subject is so meagre that only clinical observations are

valuable. Only one case of the kind, that published by Tomali, had, as far as he was aware, come to post-mortem examination, and in that case, in which there was much rigidity, the pathological findings were those of Wilson's disease.

Syphilitic Amyotrophy.

By DOUGLAS MCALPINE, M.D.

Female, aged 53, married, three living children, three others died in infancy; she has had two miscarriages.

Sixteen years ago patient noticed a weakness of her ankles and then the feet gradually dropped. This was accompanied by cramp-like pains in the legs. About thirteen years ago the left hand became weak, and later the right hand was similarly affected. The muscles of the hands wasted gradually. There is no history of tabetic pains, diplopia or sphincter trouble. The pupils are inactive to light but contract on accommodation. There is no analgesia in centre of face.

There is weakness and wasting of extensors and flexors of both fore-arms and of the intrinsic musculature of both hands, greater on the left than on the right. The fore-arm muscles react to faradism feebly, but no response to faradism can be obtained in the intrinsic muscles of either hand, and their galvanic responses are sluggish. The deep reflexes of the arms are absent. No sensory loss is present on the chest or abdomen, or on the arms.

In the lower limbs there is double foot-drop, with complete loss of power of dorsiflexion of both feet and moderate atrophy of the extensors of the feet. All other movements of both legs are strong, including plantar flexion, and no other muscles are wasted. No response to faradism can be obtained, and the response to galvanism is sluggish in the extensors of both feet. Vibration sense is diminished in both legs, but no other loss of sensation could be detected. The deep reflexes of both legs are absent; the plantar responses are flexor.

Serological findings.—Blood Wassermann reaction is feebly positive. Cerebro-spinal fluid: Wassermann reaction negative, cells 1 to 3 per c.mm., total protein 0·05 per cent., Nonne-Apelt negative, Lange curve 0000111000.

Remarks.—The diagnosis of tabes dorsalis with amyotrophy is suggested by the presence of Argyll Robertson pupils and the abolition of the deep reflexes. Against this diagnosis is the absence in the history of tabetic pains and the conservation of pain sensibility. An amyotrophic syphilitic meningo-myelitis would not account for the symmetrical wasting, and in particular the picking out of the extensors of the feet. The onset was suggestive of a polyneuritis.

Dr. CHARLES DANA (New York) said he had seen several patients with locomotor ataxy develop a muscular atrophy due probably to involvement of the anterior horns by the syphilitic virus. In many of these there were only slight electrical changes in the muscles. On the other hand the disease known clinically as progressive muscular atrophy may be superposed upon tabes. He thought the case shown belonged to this category.

Professor PETRÉN (Lund) pointed out that spinal amyotrophy due to syphilis is usually symmetrical. The absence of any increase of cells and of other characteristic change in the cerebro-spinal fluid makes the existence of tabes improbable. On the other hand the normal fluid does not exclude the possibility that a syphilitic meningitis had been responsible sixteen years ago for the wasting of the muscles.

Dr. CADWALADER (Philadelphia) said that considerable muscular wasting was often found in chronic tabes. He believed that in many of these cases the muscular wasting was due to an alcoholic multiple neuritis superimposed upon the syphilitic process. Since prohibition has been introduced into the United States it has been said—whether correctly or not he did not know—that fewer of these cases have been seen, and that this coincided with the fact that fewer chronic alcoholics are now found in hospitals. He had no doubt that in the the presence of alcoholism these amyotrophies were more likely to develop.

Dr. C. DANA said that before prohibition was adopted a large number of patients with conditions due to alcoholism were admitted each year to his hospital. On the introduction of prohibition the number went down, but now the figure was higher than in pre-prohibition days.

Dr. PURDON MARTIN (London) said that in a paper he recently wrote on this class of case, he tried to emphasize that they were clinically uncomplicated, that there were not necessarily any signs of tabes present. He saw no reason why this case should not be regarded as one of simple syphilitic amyotrophy.

Dr. MCALPINE, in reply, said that against the diagnosis of tabes was the absence of characteristic pains and analgesia. There was no evidence of any abuse of alcohol in this case.

A Case of Mimetic Facial Paralysis.

By A. FEILING.

This patient, a boy, aged 8, has a peculiar defect of innervation of the muscles of the right side of his face. It has been called "mimetic" or "mimicking" facial paralysis. While he has preserved perfectly the voluntary power to innervate his facial muscles on both sides, there was an almost complete paralysis of the right side of his face in emotional or expressional movements. When the boy smiles he appears to have an extreme right facial paralysis, chiefly of the muscles at the angle of the mouth, but of the upper part of the face too. He has also retained "associated movements," for if he is asked to show his teeth he screws up both eyes equally. This is the reverse of what is seen in the ordinary type of supra-nuclear facial paralysis.

In the literature there is little or nothing on the physiology of this condition or on the localization of the lesion responsible for it. Nothnagel, in 1879, described the condition, and assumed that it was due to some disturbance in the optic thalamus or close to it, as in one of his cases there was a large tumour occupying the thalamus on one side, but other structures were also involved.

In September, 1925, the boy had a fall, striking his right temporal region,

but he did not lose consciousness. There was no record that his limbs were paralysed, or that he suffered from headache. Fourteen days later his parents noticed that there was something wrong about his face, and a month later he had his first fit. From then until May, 1927, he had on an average one fit a month. He was admitted into hospital in May. One fit, which was observed, began abruptly without warning, his head and eyes were deviated powerfully to the right side and he became unconscious at once. The clonic movements began in his right foot, but spread rapidly to involve the right arm and leg, and later the left side of the body; they were more violent on the right side than on the left. There was no weakness of his limbs after this attack. No further attacks have occurred though the patient has not been treated by bromides or other drugs. There are no signs of organic disease, apart from the facial paralysis. The Wassermann reaction of his blood is negative, his cerebro-spinal fluid is normal, and skiagrams of the skull show nothing unusual. Dr. Sachs has, however, demonstrated while the patient was on exhibition that there was a difference in the percussion note on the two sides of the skull, the note on the right side being flatter and higher pitched. It is suggested that there is some damage to the frontal or temporal region of the left cerebral hemisphere as a result of the contrecoup effect from a blow on the opposite right temple.

Dr. WEISENBURG (Philadelphia) said he had seen a patient with a condition very similar to that in Dr. Feiling's case. Dr. Spiller, who examined the brain, found a thrombosis of the superior cerebellar artery on one side, and a softening of the cerebellum on that side which extended into the dentate nucleus; there was also a lesion in one side of the pons, above the level of the nucleus of the facial nerve. The patient had sensory disturbances on the opposite side of the body, such as would naturally result from a pontine lesion. Dr. C. K. Mills, who was interested in the isolated loss of expressional or emotional movements of one side of the face, believed it might be related to lesions in the cerebellum.

Dr. CADWALADER (Philadelphia) said that at the last meeting of the American Neurological Association Dr. Crome presented some photographs of a case which had a similar form of paralysis of the face. The explanation of the phenomenon had excited a good deal of discussion.

Dr. RUSSELL BRAIN (London) asked whether Dr. Feiling was familiar with Dr. Kinnier Wilson's paper, which suggested that there is a separate path for emotional expression, running from the frontal lobe to the facial nucleus. This path is distinct from the pyramidal system and may be consequently injured independently of it.

Dr. E. SACHS (St. Louis) drew attention to the fact that a number of years ago, while making localized lesions on the cerebral cortex, he demonstrated groups of fibres independent of the pyramidal system which ran into the thalamus.

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